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(54) Title: CIRCULARLY PERMUTED ERYTHROPOIETIN RECEPTOR AGONISTS

(57) Abstract

Disclosed are novel Erythropoietin receptor agonist proteins, DNAs which encode the Erythropoietin receptor agonist proteins, methods of making the Erythropoietin receptor agonist proteins and methods of using the Erythropoietin receptor agonist proteins.

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CIRCULARLY PERMUTED ERYTHROPOIETIN RECEPTOR AGONISTS

The present application claims priority under Title 35, United States Code, §119 of United States Provisional application Serial No. 60/034,044, filed October 25, 1996.

FIELD OF THE INVENTION

The present invention relates to human Erythropoietin (EPO) receptor agonists. These EPO receptor agonists retain one or more activities of native EPO and may also show improved hematopoietic cell-stimulating activity and/or an improved activity profile which may include reduction of undesirable biological activities associated with native EPO and/or have improved physical properties which may include increased solubility, stability and refold efficiency.

BACKGROUND OF THE INVENTION

Colony stimulating factors which stimulate the differentiation and/or proliferation of bone marrow cells have generated much interest because of their therapeutic potential for restoring depressed levels of hematopoietic stem cell-derived cells.

Erythropoietin is a naturally-occurring glycoprotein hormone with a molecular weight that was first reported to be approximately 39,000 daltons (T. Miyaki *et al.*, *J. Biol. Chem.* **252**:5558-5564 (1977)). The mature hormone is 166 amino acids long and the "prepro" form of the hormone, with its leader peptide, is 193 amino acids long (F. Lin, U.S. Patent No. 4,703,008). The mature hormone has a molecular weight, calculated from its amino acid sequence, of 18,399 daltons (K. Jacobs et al., *Nature* **313**:806-810 (1985); J. K. Browne *et al.*, *Cold Spring Harbor Symp. Quant. Biol.* **5**:1693-702 (1986).

The first mutant erythropoietins (i.e., erythropoietin analogs), prepared by making amino acid substitutions and deletions, have demonstrated reduced or unimproved activity. As described in U.S. Patent NO. 4,703,008, replacement of the tyrosine residues at positions 15, 40 and 145 with phenylalanine residues, replacement of the cysteine residue at position 7 with an histidine, substitution of the proline at position 2 with an asparagine, deletion of residues 2-6, deletion of residues 163-166, and deletion of residues 27-55 does not result in an apparent increase in biological activity. The Cys^{7}-to-His^{7} mutation eliminates biological activity. A series of mutant erythropoietins with a single amino acid substitution at asparagine residues 24, 38 or 83 show severely reduced activity (substitution at position 24) or exhibit rapid intracellular degradation and apparent lack of secretion (substitution at residue 38 or 183). Elimination of the O-linked glycosylation site at serine126 results in rapid degradation or lack of secretion of the erythropoietin analog (S. Dube *et al., J. Biol. Chem.* **33**:17516-17521 (1988). These authors conclude that glycosylation sites at residues 38, 83 and 126 are required for proper secretion and that glycosylation sites located at residues 24 and 38 may be involved in the biological activity of mature erythropoietin.

Deglycosylated erythropoietin is fully active in *in vitro* bioassays (M. S. Dorsdal et al., *Endocrinology* **116**:2293-2299 (1985); U.S. Patent No. 4,703,008; E. Tsuda *et al., Eur J. Biochem.* **266**:20434-20439 (1991). However, glycosylation of erythropoietin is widely accepted to play a critical role in the *in vivo* activity of the hormone (P. H.. Lowy *et al., Nature* **185**:102-105 (1960); E. Goldwasser and C. K. H.. Kung, *Ann. N.Y. Acad. Science* **149**:49-53 (1968); W. A. Lukowsky and R.

H.. Painter, *Can. J. Biochem.* :909-917 (1972); D.W. Briggs *et al.*, *Amer. J. Phys.* **201**:1385-1388 (1974); J.C. Schooley, *Exp. Hematol.* **13**:994-998; N. Imai *et al.*, *Eur. J. Biochem.* **194**:457-462 (1990); M.S. Dordal *et al.*, *Endocrinology* **116**:2293-2299 (1985); E. Tsuda *et al.*, *Eur. J. Biochem.* **188**:405-411 (1990); U.S. Patent No. 4,703,008; J.K. Brown *et al.*, *Cold Spring Harbor Symposia on Quant. Biol.* 51:693-702 (1986); and K. Yamaguchi *et al.*, *J. Biol. Chem.* **266**:20434-20439 (1991). The lack if *in vivo* biological activity of deglycosylated analogs of erythropoietin is attributed to a rapid clearance of the deglycosylated hormone from the circulation of treated animals. This view is supported by direct comparison of the plasma half-life of glycosylated and deglycosylated erythropoietin (J.C. Spivak and B.B. Hoyans, *Blood* **73**:90-99 (1989), and M.N. Fukuda, *et al.*, *Blood* **73**:84-89 (1989).

Oligonucleotide-directed mutagenesis of erythropoietin glycosylation sites has effectively probed the function of glycosylation but has failed, as yet, to provide insight into an effective strategy for significantly improving the characteristics of the hormone for therapeutic applications.

A series of single amino acid substitution or deletion mutants have been constructed, involving amino acid residues 15, 24, 49, 76, 78, 83, 143, 145, 160, 162, 163, 164, 165 and 166. In these mutants are altered the carboxy terminus, the glycosylation sites, and the tyrosine residues of erythropoietin. The mutants have been administered to animals while monitoring hemoglobin, hematocrit and reticulocyte levels (EP No. 0 409 113). While many of these mutants retain *in vivo* biological activity, none show a significant increase in their ability to raise hemoglobin, hematocrit or

reticulocyte (the immediate precursor of an erythrocyte) levels when compared to native erythropoietin.

Another set of mutants has been constructed to probe the function of residues 99-119 (domain 1) and residues 111-129 (domain 2) (Y. Chern *et al.*, *Eur. J. Biochem.* **202**:225-230 (1991)). The domain 1 mutants are rapidly degraded and inactive in an *in vitro* bioassay while the domain 2 mutants, at best, retain *in vitro* activity. These mutants also show no enhanced *in vivo* biological activity as compared to wild-type, human erythropoietin. These authors conclude that residues 99-119 play a critical role in the structure of erythropoietin.

The human erythropoietin molecule contains two disulfide bridges, one linking the cysteine residues at positions 7 and 161, and a second connecting cysteines at positions 29 and 33 (P.H. Lai et al., *J. Biol. Chem.* **261**:3116-3121 (1986)). Oligonucleotide-directed mutagenesis has been used to probe the function of the disulfide bridge linking cysteines 29 and 33 in human erythropoietin. The cysteine at position 33 has been converted to a proline residue, which, mimics the structure of murine erythropoietin at this residue. The resulting mutant has greatly reduced *in vitro* activity. The loss of activity is so severe that the authors conclude that the disulfide bridge between residues 29 and 33 is essential for erythropoietin function (F.K. Lin, *Molecular and Cellular Aspects of Erythropoietin and Erythropoiesis*, pp. 23-36, ed. I.N. Rich, Springer-Verlag, Berlin (1987)).

U.S. Patent No. 4,703,008 by Lin, F-K. (hereinafter referred to as "the '008 patent") speculates about a wide variety of modifications of EPO, including addition, deletion, and substitution analogs of EPO.

The '008 patent does not indicate that any of the suggested modifications would increase biological activity *per se*, although it is stated that deletion of glycosylation sites might increase the activity of EPO produced in yeast (See the '008 patent at column 37, lines 25-28). Also, the '008 patent speculates that EPO analogs which have one or more tyrosine residues replaced with phenylalanine may exhibit an increased or decreased receptor binding affinity.

Australian Patent Application No. AU-A-59145/90 by Fibi, M *et al.* also discusses a number of modified EPO proteins (EPO muteins). It is generally speculated that the alteration of amino acids 10-55, 70-85, and 130-166 of EPO. In particular, additions of positively charged basic amino acids in the carboxyl terminal region are purported to increase the biological activity of EPO.

U.S. Patent No. 4,835,260 by Shoemaker, C.B. discusses modified EPO proteins with amino acid substitutions of the methionine at position 54 and asparagine at position 38. Such EPO muteins are thought to have improved stability but are not proposed to exhibit any increase in biological activity relative to wild type EPO.

WO 91/05867 discloses analogs of human erythropoietin having a greater number of sites for carbohydrate attachment than human erythropoietin, such as EPO (Asn^{69}), EPO (Asn^{125}, Ser^{127}), EPO (Thr^{125}), and EPO (Pro^{124}, Thr^{125}).

WO 94 /24160 discloses erythropoietin muteins which have enhanced activity, specifically amino acid substitutions at positions 20, 49, 73, 140, 143, 146, 147 and 154.

WO 94/25055 discloses erythropoietin analogs, including EPO (X^{33}, Cys^{139}, des-Arg^{166}) and EPO (Cys^{139}, des-Arg^{166}).

Rearrangement of Protein Sequences

In evolution, rearrangements of DNA sequences serve an important role in generating a diversity of protein structure and function. Gene duplication and exon shuffling provide an important mechanism to rapidly generate diversity and thereby provide organisms with a competitive advantage, especially since the basal mutation rate is low (Doolittle, *Protein Science* **1**:191-200, 1992).

The development of recombinant DNA methods has made it possible to study the effects of sequence transposition on protein folding, structure and function. The approach used in creating new sequences resembles that of naturally occurring pairs of proteins that are related by linear reorganization of their amino acid sequences (Cunningham, et al., *Proc. Natl. Acad. Sci. U.S.A.* **76**:3218-3222, 1979; Teather & Erfle, *J. Bacteriol.* **172**: 3837-3841, 1990; Schimming et al., *Eur. J. Biochem.* **204**: 13-19, 1992; Yamiuchi and Minamikawa, *FEBS Lett.* **260**:127-130, 1991: MacGregor et al., *FEBS Lett.* **378**:263-266, 1996). The first in vitro application of this type of rearrangement to proteins was described by Goldenberg and Creighton (*J. Mol. Biol.* **165**:407-413, 1983). A new N-terminus is selected at an internal site (breakpoint) of the original sequence, the new sequence having the same order of amino acids as the original from the breakpoint until it reaches an amino acid that is at or near the original C-terminus. At this point the new sequence is joined, either directly or through an additional portion of sequence (linker), to an amino acid that is at or near the original N-

terminus, and the new sequence continues with the same sequence as the original until it reaches a point that is at or near the amino acid that was N-terminal to the breakpoint site of the original sequence, this residue forming the new C-terminus of the chain.

This approach has been applied to proteins which range in size from 58 to 462 amino acids (Goldenberg & Creighton, *J. Mol. Biol.* **165**:407-413, 1983; Li & Coffino, *Mol. Cell. Biol.* **13**:2377-2383, 1993). The proteins examined have represented a broad range of structural classes, including proteins that contain predominantly α -helix (interleukin-4; Kreitman et al., *Cytokine* **7**:311-318, 1995), β -sheet (interleukin-1; Horlick et al., *Protein Eng.* **5**:427-431, 1992), or mixtures of the two (yeast phosphoribosyl anthranilate isomerase; Luger et al., *Science* **243**:206-210, 1989). Broad categories of protein function are represented in these sequence reorganization studies:

Enzymes

T4 lysozyme	Zhang et al., *Biochemistry* **32**:12311-12318 (1993); Zhang et al., *Nature Struct. Biol.* **1**:434-438 (1995)
dihydrofolate reductase	Buchwalder et al., *Biochemistry* **31**:1621-1630 (1994); Protasova et al., *Prot. Eng.* **7**:1373-1377 (1995)
ribonuclease T1	Mullins et al., *J. Am. Chem. Soc.* **116**:5529-5533 (1994); Garrett et al., *Protein Science* **5**:204-211 (1996)
Bacillus β-glucanse	Hahn et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:10417-10421 (1994)

aspartate transcarbamoylase	Yang & Schachman, *Proc. Natl. Acad. Sci. U.S.A.* **90**:11980-11984 (1993)
phosphoribosyl anthranilate isomerase	Luger et al., *Science* **243**:206-210 (1989); Luger et al., *Prot. Eng.* **3**:249-258 (1990)
pepsin/pepsinogen	Lin et al., *Protein Science* **4**:159-166 (1995)
glyceraldehyde-3-phosphate dehydrogenase	Vignais et al., *Protein Science* **4**:994-1000 (1995)
ornithine decarboxylase	Li & Coffino, *Mol. Cell. Biol.* **13**:2377-2383 (1993)
yeast phosphoglycerate dehydrogenase	Ritco-Vonsovici et al., *Biochemistry* **34**:16543-16551 (1995)
Enzyme Inhibitor	
basic pancreatic trypsin inhibitor	Goldenberg & Creighton, *J. Mol. Biol.* **165**:407-413 (1983)
Cytokines	
interleukin-1β	Horlick et al., *Protein Eng.* **5**:427-431 (1992)
interleukin-4	Kreitman et al., *Cytokine* **7**:311-318 (1995)
Tyrosine Kinase Recognition Domain	

α-spectrin SH3 domain	Viguera, et al., *J. Mol. Biol.* **247**:670-681 (1995)

Transmembrane Protein

omp A	Koebnik & Krämer, *J. Mol. Biol.* **250**:617-626 (1995)

Chimeric Protein

interleukin-4–*Pseudomonas* exotoxin fusion molecule	Kreitman et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:6889-6893 (1994).

The results of these studies have been highly variable. In many cases substantially lower activity, solubility or thermodynamic stability were observed (*E. coli* dihydrofolate reductase, aspartate transcarbamoylase, phosphoribosyl anthranilate isomerase, glyceraldehyde-3-phosphate dehydrogenase, ornithine decarboxylase, omp A, yeast phosphoglycerate dehydrogenase). In other cases, the sequence rearranged protein appeared to have many nearly identical properties as its natural counterpart (basic pancreatic trypsin inhibitor, T4 lysozyme, ribonuclease T1, Bacillus β-glucanase, interleukin-1β, α -spectrin SH3 domain, pepsinogen, interleukin-4). In exceptional cases, an unexpected improvement over some properties of the natural sequence was observed, e.g., the solubility and refolding rate for rearranged α-spectrin SH3 domain sequences, and the receptor affinity and anti-tumor activity of transposed interleukin-4–*Pseudomonas* exotoxin fusion molecule (Kreitman et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:6889-6893, 1994; Kreitman et al., *Cancer Res.* **55**:3357-3363, 1995).

The primary motivation for these types of studies has been to study the role of short-range and long-range

interactions in protein folding and stability. Sequence rearrangements of this type convert a subset of interactions that are long-range in the original sequence into short-range interactions in the new sequence, and vice versa. The fact that many of these sequence rearrangements are able to attain a conformation with at least some activity is persuasive evidence that protein folding occurs by multiple folding pathways (Viguera, et al., *J. Mol. Biol.* **247**:670-681, 1995). In the case of the SH3 domain of α-spectrin, choosing new termini at locations that corresponded to β-hairpin turns resulted in proteins with slightly less stability, but which were nevertheless able to fold.

The positions of the internal breakpoints used in the studies cited here are found exclusively on the surface of proteins, and are distributed throughout the linear sequence without any obvious bias towards the ends or the middle (the variation in the relative distance from the original N-terminus to the breakpoint is ca. 10 to 80% of the total sequence length). The linkers connecting the original N- and C-termini in these studies have ranged from 0 to 9 residues. In one case (Yang & Schachman, *Proc. Natl. Acad. Sci. U.S.A.* **90**:11980-11984, 1993), a portion of sequence has been deleted from the original C-terminal segment, and the connection made from the truncated C-terminus to the original N-terminus. Flexible hydrophilic residues such as Gly and Ser are frequently used in the linkers. Viguera, et al.(*J. Mol. Biol.* **247**:670-681, 1995) compared joining the original N- and C- termini with 3- or 4-residue linkers; the 3-residue linker was less thermodynamically stable. Protasova et al. (*Protein Eng.* **7**:1373-1377, 1994) used 3- or 5-residue linkers in connecting the original N-termini of *E. coli* dihydrofolate reductase; only the 3-residue linker produced protein in good yield.

Summary of the Invention

The modified human EPO receptor agonists of the present invention can be represented by the Formula:

$$X^1-(L)_a-X^2$$

wherein;

a is 0 or 1;

X^1 is a peptide comprising an amino acid sequence corresponding to the sequence of residues n+1 through J;

X^2 is a peptide comprising an amino acid sequence corresponding to the sequence of residues 1 through n;

n is an integer ranging from 1 to J-1; and

L is a linker.

In the formula above the constituent amino acids residues of human EPO are numbered sequentially 1 through J from the amino to the carboxyl terminus. A pair of adjacent amino acids within this protein may be numbered n and n+1 respectively where n is an integer ranging from 1 to J-1. The residue n+1 becomes the new N-terminus of the new EPO receptor agonist and the residue n becomes the new C-terminus of the new EPO receptor agonist.

The present invention relates to novel EPO receptor agonists polypeptides comprising a modified EPO amino acid sequence of the following formula:

```
AlaProProArgLeuIleCysAspSerArgValLeuGluArgTyrLeuLeuGluAlaLys
                          10                  20

GluAlaGluAsnIleThrThrGlyCysAlaGluHisCysSerLeuAsnGluAsnIleThr
                          30                  40

ValProAspThrLysValAsnPheTyrAlaTrpLysArgMetGluValGlyGlnGlnAla
```

50 60

ValGluValTrpGlnGlyLeuAlaLeuLeuSerGluAlaValLeuArgGlyGlnAlaLeu
70 80

LeuValAsnSerSerGlnProTrpGluProLeuGlnLeuHisValAspLysAlaValSer
90 100

GlyLeuArgSerLeuThrThrLeuLeuArgAlaLeuGlyAlaGlnLysGluAlaIleSer
110 120

ProProAspAlaAlaSerAlaAlaProLeuArgThrIleThrAlaAspThrPheArgLys
130 140

LeuPheArgValTyrSerAsnPheLeuArgGlyLysLeuLysLeuTyrThrGlyGluAla
150 160

CysArgThrGlyAspArg
166

wherein optionally 1-6 amino acids from the N-terminus and 1-5 from the C-terminus can be deleted from said EPO receptor agonists polypeptide;

wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-termini at amino acids;

23-24	48-49	111-112
24-25	50-51	112-113
25-26	51-52	113-114
26-27	52-53	114-115
27-28	53-54	115-116
28-29	54-55	116-117
29-30	55-56	117-118
30-31	56-57	118-119
31-32	57-58	119-120
32-33	77-78	120-121
33-34	78-79	121-122
34-35	79-80	122-123
35-36	80-81	123-124
36-37	81-82	124-125
37-38	82-83	125-126
38-39	84-85	126-127
40-41	85-86	127-128
41-42	86-87	128-129
43-44	87-88	129-130
44-45	88-89	131-132
45-46	108-109	respectively; and
46-47	109-110	
47-48	110-111	

said EPO receptor agonist polypeptide may optionally be immediately preceded by (methionine^{-1}), (alanine^{-1}) or (methionine^{-2}, alanine^{-1}).

The more preferred breakpoints at which new C-terminus and N-terminus can be made are; 23-24, 24-25, 25-26, 27-28, 28-29, 29-30, 30-31, 31-32, 32-33, 33-34, 34-35, 35-36, 36-37, 37-38, 38-39, 40-41, 41-42, 42-43, 52-53, 53-54, 54-55, 55-56, 77-78, 78-79, 79-80, 80-81, 81-82, 82-83, 83-84, 84-85, 85-86, 86-87, 87-88, 88-89, 109-110, 110-111, 111-112, 112-113, 113-114, 114-115, 115-116, 116-117, 117-118, 118-119, 119-120, 120-121, 121-122, 122-123, 123-124, 124-125, 125-126, 126-127, 127-128, 128-129, 129-130, 130-131, and 131-132.

The most preferred breakpoints at which new C-terminus and N-terminus can be made are; 23-24, 24-25, 31-32, 32-33, 37-38, 38-39, 82-83, 83-84,85-86, 86-87, 87-88, 125-126, 126-127, and 131-132.

The most preferred breakpoints include glycosylationn sites, non-nuetralizing antibodies, proteolyte cleavage sites.

The EPO receptor agonists of the present invention may contain amino acid substitutions, such as those disclosed in WO 94/24160 or one or more of the glycosylation sites at Asn^{24}, Asn^{83}, and Asn^{126} are changed to other amino acids such as but not limited to Asp or Glu, deletions and/or insertions. It is also intended that the EPO receptor agonists of the present invention may also have amino acid deletions at either/or both the N- and C- termini of the original protein and or deletions from the new N- and/or C-termini of the sequence rearranged proteins in the formulas shown above.

A preferred embodiment of the present invention the linker (L) joining the N-terminus to the C-terminus is a polypeptide selected from the group consisting of:

GlyGlyGlySer SEQ ID NO:123;

GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;

GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO: 125;

SerGlyGlySerGlyGlySer SEQ ID NO:126;

GluPheGlyAsnMet SEQ ID NO:127;

GluPheGlyGlyAsnMet SEQ ID NO:128;

GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and

GlyGlySerAspMetAlaGly SEQ ID NO:130.

The present invention also encompasses recombinant human EPO receptor agonists co-administered or sequentially with one or more additional colony stimulating factors (CSF) including, cytokines, lymphokines, interleukins, hematopoietic growth factors which include but are not limited to GM-CSF, G-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, IL-1, IL-4, IL-2, IL-3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF) also known as steel factor or c-kit ligand (herein collectively referred to as "factors"). These co-administered mixtures may be characterized by having the usual activity of both of the peptides or the mixture may be further characterized by having a biological or physiological activity greater than simply the additive function of the presence of the EPO receptor agonists or the second colony stimulating factor alone. The co-administration may also provide an enhanced effect on the activity or an activity different from that expected by the presence of the EPO or the second colony stimulating factor. The co-administration may also have an improved activity profile which may include reduction

of undesirable biological activities associated with native human EPO. In addition to the list above, IL-3 variants taught in WO 94/12639 and WO 94/12638 fusion protein taught in WO 95/21197, and WO 95/21254 G-CSF receptor agonists disclosed in WO 97/12977, c-mpl receptor agonists disclosed in WO 97/12978, IL-3 receptor agonists disclosed in WO 97/12979 and multi-functional receptor agonists taught in WO 97/12985 can be co-administered with the polypeptides of the present invention. As used herein "IL-3 variants" refer to IL-3 variants taught in WO 94/12639 and WO 94/12638. As used herein "fusion proteins" refer to fusion protein taught in WO 95/21197, and WO 95/21254. As used herein "G-CSF receptor agonists" refer to G-CSF receptor agonists disclosed in WO 97/12978. As used herein "c-mpl receptor agonists" refer to c-mpl receptor agonists disclosed in WO 97/12978. As used herein "IL-3 receptor agonists" refer to IL-3 receptor agonists disclosed in WO 97/12979. As used herein "multi-functional receptor agonists" refer to multi-functional receptor agonists taught in WO 97/12985.

In addition, it is envisioned that in vitro uses would include the ability to stimulate bone marrow and blood cell activation and growth before the expanded cells are infused into patients.

It is also envisioned that uses of EPO receptor agonists of the present invention would include blood banking applications, where the EPO receptor agonists are given to a patent to increase the number of red blood cells and blood products removed from the patient, prior to some medical procedure, and the blood products stored and transfused back into the patient after the medical procedure. Additionally, it is envisioned that uses of EPO receptor agonists would include giving the EPO receptor agonists to a blood donor prior to blood

donation to increase the number of red blood cells, thereby allowing the donor to safely give more blood.

Brief Description of the Figures

Figure 1 schematically illustrates the sequence rearrangement of a protein. The N-terminus (N) and the C-terminus (C) of the native protein are joined through a linker, or joined directly. The protein is opened at a breakpoint creating a new N-terminus (new N) and a new C-terminus (new-C) resulting in a protein with a new linear amino acid sequence. A rearranged molecule may be synthesized *de novo* as linear molecule and not go through the steps of joining the original N-terminus and the C-terminus and opening of the protein at the breakpoint.

Figure 2 shows a schematic of Method I, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the amino acid 11 (a.a. 1- 10 are deleted) through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

Figure 3 shows a schematic of Method II, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined without a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the original N-terminus and a new C-terminus created at amino acid 96 of the original sequence.

Figure 4 shows a schematic of Method III, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to amino acid 1 through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

Figure 5 shows a DNA sequence encoding human mature EPO based on the sequence of Lin et al. (*PNAS* **82**:7580-7584, 1985).

Detailed Description of the Invention

Receptor agonists of the present invention may be useful in the treatment of diseases characterized by decreased levels of red blood cells of the hematopoietic system.

A EPO receptor agonist may be useful in the treatment or prevention of anemia. Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites used in chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs, phenothiazones, tranquilizers such as meprobamate, analgesics such as aminopyrine and dipyrone, anti-convulsants such as phenytoin or carbamazepine, antithyroids such as propylthiouracil and methimazole and diuretics. EPO receptor agonists may be useful in preventing or treating the bone marrow suppression or hematopoietic deficiencies which often occur in patients treated with these drugs.

Hematopoietic deficiencies may also occur as a result of viral, microbial or parasitic infections and as a result of treatment for renal disease or renal failure, e.g., dialysis. The present peptide may be useful in treating such hematopoietic deficiency.

Another aspect of the present invention provides plasmid DNA vectors for use in the method of expression of these novel EPO receptor agonists. These vectors contain the novel DNA sequences described above which code for the novel polypeptides of the invention. Appropriate vectors which can transform host cells capable of expressing the EPO receptor agonists include expression vectors comprising nucleotide sequences coding for the EPO receptor agonists joined to transcriptional and translational regulatory sequences which are selected according to the host cells used.

Vectors incorporating modified sequences as described above are included in the present invention and are useful in the production of the modified EPO receptor agonist polypeptides. The vector employed in the method also contains selected regulatory sequences in operative association with the DNA coding sequences of the invention and capable of directing the replication and expression thereof in selected host cells.

As another aspect of the present invention, there is provided a method for producing the novel family of human EPO receptor agonists. The method of the present invention involves culturing suitable cells or cell line, which has been transformed with a vector containing a DNA sequence coding for expression of the novel EPO receptor agonist polypeptide. Suitable cells or cell lines may include various strains of bacteria such as *E. coli*, yeast, mammalian cells, or insect cells may be utilized as host cells in the method of the present invention.

Other aspects of the present invention are methods and therapeutic compositions for treating the conditions referred to above. Such compositions comprise a therapeutically effective amount of one or more of the EPO receptor agonists of the present invention in a mixture with a pharmaceutically acceptable carrier. This composition can be administered either parenterally, intravenously or subcutaneously. When administered, the therapeutic composition for use in this invention is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such a parenterally acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art.

Administration will be in accordance with a dosage regimen that will be readily ascertained by the skilled,

based on *in vivo* specific activity of the analog in comparison with human erythropoietin and based on what is now known in the art concerning the administration of human erythropoietin for inducing erythropoiesis and treating various conditions, such as anemia, in humans, including anemia in patients suffering from renal failure. Dosage of an analog of the invention may vary somewhat from individual to individual, depending on the particular analog and its specific *in vivo* activity, the route of administration, the medical condition, age, weight or sex of the patient, the patient's sensitivities to the analog or components of vehicle, and other factors which the attending physician will be capable of readily taking into account. With regard to therapeutic uses of analogs of the invention, reference is made to U.S. Patent Nos. 4,703,008 and 4,835,260; *see also* the chapter on (recombinant) [des-Arg^{166}]human erythropoietin at pages 591-595 of the Physicians' Desk Commercially available preparations of recombinant [des-Arg^{166}] human erythropoietin have 2,000, 3,000, 4,000 or 10,000 units of the glycohormone per mL in preservative-free aqueous solution with 2.5 mg/mL human serum albumin, 5.8 mg/mL sodium citrate, 5.8 mg/mL NaCl, and 0.06 mg/mL citric acid, pH 6.9 (+/-0.3).

Recombinantly produced EPO has proven especially useful for the treatment of patients suffering from impaired red blood cell production (Physicians Desk Reference (PDR). 1993 edition, pp 602-605). Recombinant EPO has proven effective in treating anemia associated with chronic renal failure and HIV-Infected individuals suffering from lowered endogenous EPO levels related to therapy with Zidovudine (AZT) (See PDR, 1993 edition, at page 6002).

Modifications of the EPO protein which would improve its utility as a tool for diagnosis or treatment

of blood disorders are certainly desirable. In particular, modified forms of EPO exhibiting enhanced biological activity would be more effective and efficient than native EPO in the therapy setting when it is necessary to administer EPO to the patient, enabling administration less frequently and/or at a lower dose. Administration of reduced amounts of EPO would also presumably reduce the risk of adverse effects associated with EPO treatment, such as hypertension, seizures, headaches, etc. (See PDR, 1993 edition, at pp. 603-604). The EPO receptor agonists of the present invention may also have improved stability and hence increased half-life which would allow for the production of a non-glycosylated form of EPO in a bacterial expression system at a much lower cost. Due it's increased half-life this non-glycosylated form of EPO would have an increased in vivo activity compared de-glycosylated EPO.

The therapeutic method and compositions may also include co-administration with other hematopoietic factors. A non-exclusive list of other appropriate hematopoietins, colony stimulating factors (CSFs) and interleukins for simultaneous or serial co-administration with the polypeptides of the present invention includes GM-CSF, G-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, IL-1, IL-4, IL-2, IL-3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF) also known as steel factor or c-kit ligand (herein collectively referred to as "factors"), or combinations thereof. In addition to the list above, IL-3 variants taught in WO 94/12639 and WO 94/12638 fusion protein taught in WO 95/21197, and WO 95/21254 G-CSF receptor agonists disclosed in WO 97/12977, c-mpl receptor agonists disclosed in WO 97/12978, IL-3 receptor

agonists disclosed in WO 97/12979 and multi-functional receptor agonists taught in WO 97/12985 can be co-administered with the polypeptides of the present invention.

The EPO receptor agonists of the present invention may be useful in the mobilization of hematopoietic progenitors and stem cells in peripheral blood. Peripheral blood derived progenitors have been shown to be effective in reconstituting patients in the setting of autologous marrow transplantation.

The EPO receptor agonists of the present invention may also be useful in the ex vivo expansion of hematopoietic progenitors. Colony stimulating factors (CSFs), such as G-CSF, have been administered alone, co-administered with other CSFs, or in combination with bone marrow transplants subsequent to high dose chemotherapy to treat the anemia, neutropenia and thrombocytopenia which are often the result of such treatment.

Another aspect of the invention provides methods of sustaining and/or expanding hematopoietic precursor cells which includes inoculating the cells into a culture vessel which contains a culture medium that has been conditioned by exposure to a stromal cell line such as HS-5 (WO 96/02662, Roecklein and Torok-Strob, *Blood* **85**:997-1105, 1995) that has been supplemented with a EPO receptor agonist of the present invention.

Determination of the Linker

The length of the amino acid sequence of the linker can be selected empirically or with guidance from structural information, or by using a combination of the two approaches.

When no structural information is available, a small series of linkers can be prepared for testing using a design whose length is varied in order to span a range from 0 to 50 Å and whose sequence is chosen in order to be consistent with surface exposure (hydrophilicity, Hopp & Woods, *Mol. Immunol.* **20**: 483-489, 1983; Kyte & Doolittle, *J. Mol. Biol.* **157**:105-132, 1982; solvent exposed surface area, Lee & Richards, *J. Mol. Biol.* **55**:379-400, 1971) and the ability to adopt the necessary conformation without deranging the configuration of the EPO receptor agonist (conformationally flexible; Karplus & Schulz, *Naturwissenschaften* **72**:212-213, (1985). Assuming an average of translation of 2.0 to 3.8 Å per residue, this would mean the length to test would be between 0 to 30 residues, with 0 to 15 residues being the preferred range. Exemplary of such an empirical series would be to construct linkers using a cassette sequence such as Gly-Gly-Gly-Ser repeated n times, where n is 1, 2, 3 or 4. Those skilled in the art will recognize that there are many such sequences that vary in length or composition that can serve as linkers with the primary consideration being that they be neither excessively long nor short (cf., Sandhu, *Critical Rev. Biotech.* **12**: 437-462, 1992); if they are too long, entropy effects will likely destabilize the three-dimensional fold, and may also make folding kinetically impractical, and if they are too short, they will likely destabilize the molecule because of torsional or steric strain.

Those skilled in the analysis of protein structural information will recognize that using the distance between the chain ends, defined as the distance between the c-alpha carbons, can be used to define the length of the sequence to be used, or at least to limit the number of possibilities that must be tested in an empirical selection of linkers. They will also recognize that it

is sometimes the case that the positions of the ends of the polypeptide chain are ill-defined in structural models derived from x-ray diffraction or nuclear magnetic resonance spectroscopy data, and that when true, this situation will therefore need to be taken into account in order to properly estimate the length of the linker required. From those residues whose positions are well defined are selected two residues that are close in sequence to the chain ends, and the distance between their c-alpha carbons is used to calculate an approximate length for a linker between them. Using the calculated length as a guide, linkers with a range of number of residues (calculated using 2 to 3.8Å per residue) are then selected. These linkers may be composed of the original sequence, shortened or lengthened as necessary, and when lengthened the additional residues may be chosen to be flexible and hydrophilic as described above; or optionally the original sequence may be substituted for using a series of linkers, one example being the "Gly-Gly-Gly-Ser" cassette approach mentioned above; or optionally a combination of the original sequence and new sequence having the appropriate total length may be used.

Determination of the Amino and Carboxyl Termini of EPO Receptor Agonists

Sequences of EPO receptor agonists capable of folding to biologically active states can be prepared by appropriate selection of the beginning (amino terminus) and ending (carboxyl terminus) positions from within the original polypeptide chain while using the linker sequence as described above. Amino and carboxyl termini are selected from within a common stretch of sequence, referred to as a breakpoint region, using the guidelines described below. A novel amino acid sequence is thus generated by selecting amino and carboxyl termini from

within the same breakpoint region. In many cases the selection of the new termini will be such that the original position of the carboxyl terminus immediately preceded that of the amino terminus. However, those skilled in the art will recognize that selections of termini anywhere within the region may function, and that these will effectively lead to either deletions or additions to the amino or carboxyl portions of the new sequence.

It is a central tenet of molecular biology that the primary amino acid sequence of a protein dictates folding to the three-dimensional structure necessary for expression of its biological function. Methods are known to those skilled in the art to obtain and interpret three-dimensional structural information using x-ray diffraction of single protein crystals or nuclear magnetic resonance spectroscopy of protein solutions. Examples of structural information that are relevant to the identification of breakpoint regions include the location and type of protein secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets, chain reversals and turns, and loops; Kabsch & Sander, *Biopolymers* **22**: 2577-2637, 1983; the degree of solvent exposure of amino acid residues, the extent and type of interactions of residues with one another (Chothia, *Ann. Rev. Biochem.* **53**:537-572; 1984) and the static and dynamic distribution of conformations along the polypeptide chain (Alber & Mathews, *Methods Enzymol.* **154**: 511-533, 1987). In some cases additional information is known about solvent exposure of residues; one example is a site of post-translational attachment of carbohydrate which is necessarily on the surface of the protein. When experimental structural information is not available, or is not feasible to obtain, methods are also available to analyze the primary amino acid sequence in order to make predictions of protein tertiary and secondary structure, solvent accessibility

and the occurrence of turns and loops. Biochemical methods are also sometimes applicable for empirically determining surface exposure when direct structural methods are not feasible; for example, using the identification of sites of chain scission following limited proteolysis in order to infer surface exposure (Gentile & Salvatore, *Eur. J. Biochem.* **218**:603-621, 1993)

Thus using either the experimentally derived structural information or predictive methods (e.g., Srinivisan & Rose *Proteins: Struct., Funct. & Genetics*, **22**: 81-99, 1995) the parental amino acid sequence is inspected to classify regions according to whether or not they are integral to the maintenance of secondary and tertiary structure. The occurrence of sequences within regions that are known to be involved in periodic secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets) are regions that should be avoided. Similarly, regions of amino acid sequence that are observed or predicted to have a low degree of solvent exposure are more likely to be part of the so-called hydrophobic core of the protein and should also be avoided for selection of amino and carboxyl termini. In contrast, those regions that are known or predicted to be in surface turns or loops, and especially those regions that are known not to be required for biological activity, are the preferred sites for location of the extremes of the polypeptide chain. Continuous stretches of amino acid sequence that are preferred based on the above criteria are referred to as a breakpoint region.

Materials and Methods

Recombinant DNA methods

Unless noted otherwise, all specialty chemicals were obtained from Sigma Co., (St. Louis, MO). Restriction endonucleases and T4 DNA ligase were

obtained from New England Biolabs (Beverly, MA) or Boehringer Mannheim (Indianapolis, IN).

Transformation of *E. coli* strains

E. coli strains, such as DH5α™ (Life Technologies, Gaithersburg, MD) and TG1 (Amersham Corp., Arlington Heights, IL) are used for transformation of ligation reactions and are the source of plasmid DNA for transfecting mammalian cells. *E. coli* strains, such as MON105 and JM101, can be used for expressing the EPO receptor agonist of the present invention in the cytoplasm or periplasmic space.

MON105 ATCC#55204: F-, lamda-,IN(rrnD, rrE)1, rpoD+, rpoH358

DH5α™: F-, phi80dlacZdeltaM15, delta(lacZYA-argF)U169, deoR, recA1, endA1, hsdR17(rk-,mk+), phoA, supE44lamda-, thi-1, gyrA96, relA1

TG1: delta(lac-pro), supE, thi-1, hsdD5/F'(traD36, proA+B+, lacIq, lacZdeltaM15)

DH5α™ Subcloning efficiency cells are purchased as competent cells and are ready for transformation using the manufacturer's protocol, while both *E. coli* strains TG1 and MON105 are rendered competent to take up DNA using a $CaCl_2$ method. Typically, 20 to 50 mL of cells are grown in LB medium (1% Bacto-tryptone, 0.5% Bacto-yeast extract, 150 mM NaCl) to a density of approximately 1.0 optical density unit at 600 nanometers (OD600) as measured by a Baush & Lomb Spectronic spectrophotometer (Rochester, NY). The cells are collected by centrifugation and resuspended in one-fifth culture volume of $CaCl_2$ solution (50 mM $CaCl_2$, 10 mM Tris-Cl, pH7.4) and are held at 4°C for 30 minutes. The

cells are again collected by centrifugation and resuspended in one-tenth culture volume of $CaCl_2$ solution. Ligated DNA is added to 0.2mL of these cells, and the samples are held at 4°C for 1 hour. The samples are shifted to 42°C for two minutes and 1mL of LB is added prior to shaking the samples at 37°C for one hour. Cells from these samples are spread on plates (LB medium plus 1.5% Bacto-agar) containing either ampicillin (100 micrograms/mL, ug/mL) when selecting for ampicillin-resistant transformants, or spectinomycin (75 ug/mL) when selecting for spectinomycin-resistant transformants. The plates are incubated overnight at 37°C. Single colonies are picked, grown in LB supplemented with appropriate antibiotic for 6-16 hours at 37°C with shaking. Colonies are picked and inoculated into LB plus appropriate antibiotic (100 ug/mL ampicillin or 75 ug/mL spectinomycin) and are grown at 37°C while shaking. Before harvesting the cultures, 1 ul of cells are analyzed by PCR for the presence of a EPO receptor agonist gene. The PCR is carried out using a combination of primers that anneal to the EPO receptor agonist gene and/or vector. After the PCR is complete, loading dye is added to the sample followed by electrophoresis as described earlier. A gene has been ligated to the vector when a PCR product of the expected size is observed.

Methods for creation of genes with new N-terminus/C-terminus

Method I. Creation of genes with new N-terminus/C-terminus which contain a linker region.

Genes with new N-terminus/C-terminus which contain a linker region separating the original C-terminus and N-terminus can be made essentially following the method described in L. S. Mullins, et al *J. Am. Chem. Soc.* **116**,

5529-5533 (1994). Multiple steps of polymerase chain reaction (PCR) amplifications are used to rearrange the DNA sequence encoding the primary amino acid sequence of the protein. The steps are illustrated in Figure 2.

In the first step, the primer set ("new start" and "linker start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein followed by the linker that connects the C-terminal and N-terminal ends of the original protein. In the second step, the primer set ("new stop" and "linker stop") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Stop") that encodes the same linker as used above, followed by the new C-terminal portion of the new protein. The "new start" and "new stop" primers are designed to include the appropriate restriction enzyme recognition sites which allow cloning of the new gene into expression plasmids. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM $MgCl_2$. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT).

"Fragment Start" and "Fragment Stop", which have complementary sequence in the linker region and the coding sequence for the two amino acids on both sides of the linker, are joined together in a third PCR step to make the full-length gene encoding the new protein. The

DNA fragments "Fragment Start" and "Fragment Stop" are resolved on a 1% TAE gel, stained with ethidium bromide and isolated using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined in equimolar quantities, heated at 70°C for ten minutes and slow cooled to allow annealing through their shared sequence in "linker start" and "linker stop". In the third PCR step, primers "new start" and "new stop" are added to the annealed fragments to create and amplify the full-length new N-terminus/C-terminus gene. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 60°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and approximately 0.5 ug of DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM $MgCl_2$. PCR reactions are purified using a Wizard PCR Preps kit (Promega).

Method II. Creation of genes with new N-terminus/C-terminus without a linker region.

New N-terminus/C-terminus genes without a linker joining the original N-terminus and C-terminus can be made using two steps of PCR amplification and a blunt end ligation. The steps are illustrated in Figure 3. In the first step, the primer set ("new start" and "P-bl start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein. In the second step, the primer set ("new stop" and "P-bl stop") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Stop") that contains the sequence encoding the new C-terminal portion of the new

protein. The "new start" and "new stop" primers are designed to include appropriate restriction sites which allow cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for 45 seconds and 72°C extension for 45 seconds. Deep Vent polymerase (New England Biolabs) is used to reduce the occurrence of overhangs in conditions recommended by the manufacturer. The "P-bl start" and "P-bl stop" primers are phosphorylated at the 5' end to aid in the subsequent blunt end ligation of "Fragment Start" and "Fragment Stop" to each other. A 100 ul reaction contained 150 pmole of each primer and one ug of template DNA; and 1x Vent buffer (New England Biolabs), 300 uM dGTP, 300 uM dATP, 300 uM dTTP, 300 uM dCTP, and 1 unit Deep Vent polymerase. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reaction products are purified using a Wizard PCR Preps kit (Promega).

The primers are designed to include appropriate restriction enzyme recognition sites which allow for the cloning of the new gene into expression vectors. Typically "Fragment Start" is designed to create a NcoI restriction site , and "Fragment Stop" is designed to create a HindIII restriction site. Restriction digest reactions are purified using a Magic DNA Clean-up System kit (Promega). Fragments Start and Stop are resolved on a 1% TAE gel, stained with ethidium bromide and isolated using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined with and annealed to the ends of the ~ 3800 base pair NcoI/HindIII vector fragment of pMON3934 by heating at 50°C for ten minutes and allowed to slow cool. The three fragments are ligated together using T4 DNA ligase (Boehringer Mannheim). The result is a plasmid containing the full-length new N-terminus/C-terminus gene. A portion of the ligation reaction is

used to transform *E. coli* strain DH5α cells (Life Technologies, Gaithersburg, MD). Plasmid DNA is purified and sequence confirmed as below.

Method III. Creation of new N-terminus/C-terminus genes by tandem-duplication method

New N-terminus/C-terminus genes can be made based on the method described in R. A. Horlick, et al *Protein Eng.* **5**:427-431 (1992). Polymerase chain reaction (PCR) amplification of the new N-terminus/C-terminus genes is performed using a tandemly duplicated template DNA. The steps are illustrated in Figure 4.

The tandemly-duplicated template DNA is created by cloning and contains two copies of the gene separated by DNA sequence encoding a linker connecting the original C- and N-terminal ends of the two copies of the gene. Specific primer sets are used to create and amplify a full-length new N terminus/C-terminus gene from the tandemly-duplicated template DNA. These primers are designed to include appropriate restriction sites which allow for the cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit (Perkin Elmer Corporation, Norwalk, CT) is used. A 100 ul reaction contains 100 pmole of each primer and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM $MgCl_2$. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reactions are purified using a Wizard PCR Preps kit (Promega).

DNA isolation and characterization

Plasmid DNA can be isolated by a number of different methods and using commercially available kits known to those skilled in the art. A few such methods are shown herein. Plasmid DNA is isolated using the Promega Wizard™ Miniprep kit (Madison, WI), the Qiagen QIAwell Plasmid isolation kits (Chatsworth, CA) or Qiagen Plasmid Midi kit. These kits follow the same general procedure for plasmid DNA isolation. Briefly, cells are pelleted by centrifugation (5000 x g), plasmid DNA released with sequential NaOH/acid treatment, and cellular debris is removed by centrifugation (10000 x g). The supernatant (containing the plasmid DNA) is loaded onto a column containing a DNA-binding resin, the column is washed, and plasmid DNA eluted with TE. After screening for the colonies with the plasmid of interest, the *E. coli* cells are inoculated into 50-100 mLs of LB plus appropriate antibiotic for overnight growth at 37°C in an air incubator while shaking. The purified plasmid DNA is used for DNA sequencing, further restriction enzyme digestion, additional subcloning of DNA fragments and transfection into mammalian, *E. coli* or other cells.

Sequence confirmation.

Purified plasmid DNA is resuspended in dH_2O and quantitated by measuring the absorbance at 260/280 nm in a Bausch and Lomb Spectronic 601 UV spectrometer. DNA samples are sequenced using ABI PRISM™ DyeDeoxy™ terminator sequencing chemistry (Applied Biosystems Division of Perkin Elmer Corporation, Lincoln City, CA) kits (Part Number 401388 or 402078) according to the manufacturers suggested protocol usually modified by the addition of 5% DMSO to the sequencing mixture. Sequencing reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT)

following the recommended amplification conditions. Samples are purified to remove excess dye terminators with Centri-Sep™ spin columns (Princeton Separations, Adelphia, NJ) and lyophilized. Fluorescent dye labeled sequencing reactions are resuspended in deionized formamide, and sequenced on denaturing 4.75% polyacrylamide-8M urea gels using an ABI Model 373A automated DNA sequencer. Overlapping DNA sequence fragments are analyzed and assembled into master DNA contigs using Sequencher v2.1 DNA analysis software (Gene Codes Corporation, Ann Arbor, MI).

Expression of EPO receptor agonists in mammalian cells

Mammalian Cell Transfection/Production of Conditioned Media

The BHK-21 cell line can be obtained from the ATCC (Rockville, MD). The cells are cultured in Dulbecco's modified Eagle media (DMEM/high-glucose), supplemented to 2mM (mM) L-glutamine and 10% fetal bovine serum (FBS). This formulation is designated BHK growth media. Selective media is BHK growth media supplemented with 453 units/mL hygromycin B (Calbiochem, San Diego, CA). The BHK-21 cell line was previously stably transfected with the HSV transactivating protein VP16, which transactivates the IE110 promoter found on the plasmid pMON3359 (See Hippenmeyer et al., *Bio/Technology*, pp.1037-1041, 1993). The VP16 protein drives expression of genes inserted behind the IE110 promoter. BHK-21 cells expressing the transactivating protein VP16 are designated BHK-VP16. The plasmid pMON1118 (See Highkin et al., *Poultry Sci.*, **70**: 970-981, 1991) expresses the hygromycin resistance gene from the SV40 promoter. A similar plasmid is available from ATCC, pSV2-hph.

BHK-VP16 cells are seeded into a 60 millimeter (mm) tissue culture dish at 3 X 10^5 cells per dish 24 hours

prior to transfection. Cells are transfected for 16 hours in 3 mL of "OPTIMEM"™ (Gibco-BRL, Gaithersburg, MD) containing 10 ug of plasmid DNA containing the gene of interest, 3 ug hygromycin resistance plasmid, pMON1118, and 80 ug of Gibco-BRL "LIPOFECTAMINE"™ per dish. The media is subsequently aspirated and replaced with 3 mL of growth media. At 48 hours post-transfection, media from each dish is collected and assayed for activity (transient conditioned media). The cells are removed from the dish by trypsin-EDTA, diluted 1:10 and transferred to 100 mm tissue culture dishes containing 10 mL of selective media. After approximately 7 days in selective media, resistant cells grow into colonies several millimeters in diameter. The colonies are removed from the dish with filter paper (cut to approximately the same size as the colonies and soaked in trypsin/EDTA) and transferred to individual wells of a 24 well plate containing 1 mL of selective media. After the clones are grown to confluence, the conditioned media is re-assayed, and positive clones are expanded into growth media.

Expression of EPO receptor agonists in *E. coli*

E. coli strain MON105 or JM101 harboring the plasmid of interest are grown at 37°C in M9 plus casamino acids medium with shaking in a air incubator Model G25 from New Brunswick Scientific (Edison, New Jersey). Growth is monitored at OD600 until it reaches a value of 1, at which time nalidixic acid (10 milligrams/mL) in 0.1 N NaOH is added to a final concentration of 50 µg/mL. The cultures are then shaken at 37°C for three to four additional hours. A high degree of aeration is maintained throughout culture period in order to achieve maximal production of the desired gene product. The cells are examined under a light microscope for the presence of inclusion bodies

(IB). One mL aliquots of the culture are removed for analysis of protein content by boiling the pelleted cells, treating them with reducing buffer and electrophoresis via SDS-PAGE (see Maniatis et al. Molecular Cloning: A Laboratory Manual, 1982). The culture is centrifuged (5000 x g) to pellet the cells.

Additional strategies for achieving high-level expression of genes in E. coli can be found in Savvas, C.M. (*Microbiological Reviews* **60**;512-538, 1996).

Inclusion Body preparation, Extraction, Refolding, Dialysis, DEAE Chromatography, and Characterization of the EPO receptor agonists which accumulate as inclusion bodies in *E. coli*.

Isolation of Inclusion Bodies:

The cell pellet from a 330 mL *E. coli* culture is resuspended in 15 mL of sonication buffer (10 mM 2-amino-2-(hydroxymethyl) 1,3-propanediol hydrochloride (Tris-HCl), pH 8.0 + 1 mM ethylenediaminetetraacetic acid (EDTA)). These resuspended cells are sonicated using the microtip probe of a Sonicator Cell Disruptor (Model W-375, Heat Systems-Ultrasonics, Inc., Farmingdale, New York). Three rounds of sonication in sonication buffer followed by centrifugation are employed to disrupt the cells and wash the inclusion bodies (IB). The first round of sonication is a 3 minute burst followed by a 1 minute burst, and the final two rounds of sonication are for 1 minute each.

Extraction and refolding of proteins from inclusion body pellets:

Following the final centrifugation step, the IB pellet is resuspended in 10 mL of 50 mM Tris-HCl, pH 9.5, 8 M urea and 5 mM dithiothreitol (DTT) and stirred at room temperature for approximately 45 minutes to allow for denaturation of the expressed protein.

The extraction solution is transferred to a beaker containing 70 mL of 5mM Tris-HCl, pH 9.5 and 2.3 M urea and gently stirred while exposed to air at 4°C for 18 to 48 hours to allow the proteins to refold. Refolding is monitored by analysis on a Vydac (Hesperia, Ca.) C18 reversed phase high pressure liquid chromatography (RP-HPLC) column (0.46x25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed to monitor the refold. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Denatured proteins generally elute later in the gradient than the refolded proteins.

Purification:

Following the refold, contaminating *E. coli* proteins are removed by acid precipitation. The pH of the refold solution is titrated to between pH 5.0 and pH 5.2 using 15% (v/v) acetic acid (HOAc). This solution is stirred at 4°C for 2 hours and then centrifuged for 20 minutes at 12,000 x g to pellet any insoluble protein.

The supernatant from the acid precipitation step is dialyzed using a Spectra/Por 3 membrane with a molecular weight cut off (MWCO) of 3,500 daltons. The dialysis is against 2 changes of 4 liters (a 50-fold excess) of 10mM Tris-HCl, pH 8.0 for a total of 18 hours. Dialysis lowers the sample conductivity and removes urea prior to DEAE chromatography. The sample is then centrifuged (20 minutes at 12,000 x g) to pellet any insoluble protein following dialysis.

A Bio-Rad Bio-Scale DEAE2 column (7 x 52 mm) is used for ion exchange chromatography. The column is equilibrated in a buffer containing 10mM Tris-HCl, pH 8.0. The protein is eluted using a 0-to-500 mM sodium chloride (NaCl) gradient, in equilibration buffer, over 45 column volumes. A flow rate of 1 mL per minute is used throughout the run. Column fractions (2 mL per fraction) are collected across the gradient and analyzed by RP HPLC on a Vydac (Hesperia, Ca.) C18 column (0.46 x 25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Pooled fractions are then dialyzed against 2 changes of 4 liters (50-to-500-fold excess) of 10 mM ammonium acetate (NH_4Ac), pH 4.0 for a total of 18 hours. Dialysis is performed using a Spectra/Por 3 membrane with a MWCO of 3,500 daltons. Finally, the sample is sterile filtered using a 0.22µm syringe filter (µStar LB syringe filter, Costar, Cambridge, Ma.), and stored at 4°C.

In some cases the folded proteins can be affinity purified using affinity reagents such as mAbs or receptor subunits attached to a suitable matrix. Alternatively, (or in addition) purification can be accomplished using any of a variety of chromatographic methods such as: ion exchange, gel filtration or hydrophobic chromatography or reversed phase HPLC.

These and other protein purification methods are described in detail in Methods in Enzymology, Volume 182 'Guide to Protein Purification' edited by Murray Deutscher, Academic Press, San Diego, CA (1990).

Protein Characterization:

The purified protein is analyzed by RP-HPLC, electrospray mass spectrometry, and SDS-PAGE. The

protein quantitation is done by amino acid composition, RP-HPLC, and Bradford protein determination. In some cases tryptic peptide mapping is performed in conjunction with electrospray mass spectrometry to confirm the identity of the protein.

Methylcellulose Assay

This assay reflects the ability of colony stimulating factors to stimulate normal bone marrow cells to produce different types of hematopoietic colonies *in vitro* (Bradley et al., *Aust. Exp Biol. Sci.* **44**:287-300, 1966), Pluznik et al., *J. Cell Comp. Physio* **66**:319-324, 1965).

Methods

Approximately 30 mL of fresh, normal, healthy bone marrow aspirate are obtained from individuals following informed consent. Under sterile conditions samples are diluted 1:5 with a 1X PBS (#14040.059 Life Technologies, Gaithersburg, MD.) solution in a 50 mL conical tube (#25339-50 Corning, Corning MD). Ficoll (Histopaque 1077 Sigma H-8889) is layered under the diluted sample and centrifuged, 300 x g for 30 min. The mononuclear cell band is removed and washed two times in 1X PBS and once with 1% BSA PBS (CellPro Co., Bothel, WA). Mononuclear cells are counted and CD34+ cells are selected using the Ceprate LC (CD34) Kit (CellPro Co., Bothel, WA) column. This fractionation is performed since all stem and progenitor cells within the bone marrow display CD34 surface antigen.

Cultures are set up in triplicate with a final volume of 1.0 mL in a 35 X 10 mm petri dish (Nunc#174926). Culture medium is purchased from Terry Fox Labs. (HCC-4230 medium (Terry Fox Labs, Vancouver, B.C., Canada) and erythropoietin (Amgen, Thousand Oaks, CA.) is added

to the culture media. 3,000-10,000 CD34+ cells are added per dish. EPO receptor agonist proteins, in conditioned media from transfected mammalian cells or purified from conditioned media from transfected mammalian cells or *E. coli*, are added to give final concentrations ranging from .001 nM to 10 nM. Cultures are resuspended using a 3cc syringe and 1.0 mL is dispensed per dish. Control (baseline response) cultures received no colony stimulating factors. Positive control cultures received conditioned media (PHA stimulated human cells: Terry Fox Lab. H2400). Cultures are incubated at 37°C, 5% CO_2 in humidified air.

Hematopoietic colonies which are defined as greater than 50 cells are counted on the day of peak response (days 10-11) using a Nikon inverted phase microscope with a 40x objective combination. Groups of cells containing fewer than 50 cells are referred to as clusters. Alternatively colonies can be identified by spreading the colonies on a slide and stained or they can be picked, resuspended and spun onto cytospin slides for staining.

Human Cord Blood Hematopoietic Growth Factor Assays

Bone marrow cells are traditionally used for in vitro assays of hematopoietic colony stimulating factor (CSF) activity. However, human bone marrow is not always available, and there is considerable variability between donors. Umbilical cord blood is comparable to bone marrow as a source of hematopoietic stem cells and progenitors (Broxmeyer et al., *PNAS USA* **89**:4109-113, 1992; Mayani et al., *Blood* **81**:3252-3258, 1993). In contrast to bone marrow, cord blood is more readily available on a regular basis. There is also a potential to reduce assay variability by pooling cells obtained fresh from several donors, or to create a bank of

cryopreserved cells for this purpose. By modifying the culture conditions, and/or analyzing for lineage specific markers, it is be possible to assay specifically for burst forming colonies (BFU-E) activity.

Methods

Mononuclear cells (MNC) are isolated from cord blood within 24 hr. of collection, using a standard density gradient (1.077 g/mL Histopaque). Cord blood MNC have been further enriched for stem cells and progenitors by several procedures, including immunomagnetic selection for CD14-, CD34+ cells; panning for SBA-, CD34+ fraction using coated flasks from Applied Immune Science (Santa Clara, CA); and CD34+ selection using a CellPro (Bothell, WA) avidin column. Either freshly isolated or cryopreserved CD34+ cell enriched fractions are used for the assay. Duplicate cultures for each serial dilution of sample (concentration range from 1 pM to 1204 pM) are prepared with 1x104 cells in 1ml of 0.9% methylcellulose containing medium without additional growth factors (Methocult H4230 from Stem Cell Technologies, Vancouver, BC.). After culturing for 7-9 days, colonies containing >30 cells are counted.

Transfected cell lines:

Cell lines, such as BHK or the murine pro B cell line Baf/3, can be transfected with a colony stimulating factor receptor, such as the human EPO receptor which the cell line does not have. These transfected cell lines can be used to determine the cell proliferative activity and/or receptor binding.

EXAMPLE 1

Genes encoding the sequence rearranged EPO ligands can be constructed by any one of the methods described herein or by other recombinant methods known to those

skilled in the art. For the purpose of this example, the site of permutation is between residues 131(Arg) and 132(Thr) of EPO. This is a site which is susceptible to proteolytic cleavage, thereby indicating surface exposure with a relatively high degree of flexibility.

In this example a new N-terminus and a new C-terminus is created without a linker joining the original termini. This is done, as described in Method II, in 2 steps of PCR and a blunt end ligation.

In the first PCR step, using a vector containing the DNA sequence of SEQ ID NO:120 as the template, and the primers "new start" and "blunt start", a DNA fragment is created which encodes the new N-terminus. This fragment is termed "fragment start". The sequence underlined in the new start primer is the NcoI restriction site.

New start primer = gcgcgcCCATGGACAATCACTGCTGAC SEQ ID NO:131
Blunt start primer = TCTGTCCCCTGTCCT SEQ ID NO:132

In the second PCR step, using a vector containing the DNA sequence of SEQ ID NO:120 as the template, and the primers "new stop" and "blunt stop" create a DNA fragment which encodes the new C-terminus. This fragment is termed "fragment stop". The sequence underlined in the new stop primer is the HindIII restriction site.

New stop primer = gcgcgcAAGCTTATTATCGGAGTGGAGCAGCTGAGGCCGCATC SEQ ID NO:133

Blunt end primer = GCCCCACCACGCCTCATCTGT SEQ ID NO:134

In the ligation step, the two fragments created in the two PCR reactions are ligated together, digested with NcoI and HindIII and cloned into an expression vector. The clones are screened by restiction analysis and DNA sequenced to confirm the proper sequence. The primers can be designed to create restriction sites other than NcoI and HindIII to clone into other expression vectors.

EXAMPLE 2

The sequence rearranged EPO receptor agonists of the present invention can be assayed for bioactivity by the methods described herein or by other assays know to those skilled in the art.

Additional techniques for the construction of the variant genes, recombinant protein expression , protein purification, protein characterization, biological activity determination can be found in WO 94/12639, WO 94/12638, WO 95/20976, WO 95/21197, WO 95/20977, WO 95/21254 which are hereby incorporated by reference in their entirety.

All references, patents or applications cited herein are incorporated by reference in their entirety as if written herein.

Various other examples will be apparent to the person skilled in the art after reading the present disclosure without departing from the spirit and scope of the invention. It is intended that all such other examples be included within the scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANT: G. D. Searle and Company

(ii) TITLE OF THE INVENTION: Novel Erythropoietin Receptor Agonists

(iii) NUMBER OF SEQUENCES: 134

(iv) CORRESPONDENCE ADDRESS:
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(B) STREET: P.O. Box 5110
(C) CITY: Chicago
(D) STATE: IL
(E) COUNTRY: U. S. A.
(F) ZIP: 60680

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ for Windows Version 2.0

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 21-OCT-1997
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 60/034,044
(B) FILING DATE: 25-OCT-1996

(viii) ATTORNEY/AGENT INFORMATION:
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(B) REGISTRATION NUMBER: 34,547
(C) REFERENCE/DOCKET NUMBER: 2991/1

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(A) TELEPHONE: 314-737-6986
(B) TELEFAX: 314-737-6972
(C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
 1               5                  10                  15
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
            20                  25                  30
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
        35                  40                  45
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
    50                  55                  60
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
65                  70                  75                  80
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
                85                  90                  95
Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala
            100                 105                 110
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly
        115                 120                 125
```

```
Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly
    130                 135                 140
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu
145                 150                 155                 160
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
 1               5                  10                  15
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
            20                  25                  30
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
        35                  40                  45
Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
    50                  55                  60
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
65                  70                  75                  80
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
                85                  90                  95
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
            100                 105                 110
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
        115                 120                 125
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
    130                 135                 140
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
145                 150                 155                 160
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val
 1               5                  10                  15
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
            20                  25                  30
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
        35                  40                  45
Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu
    50                  55                  60
Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu
65                  70                  75                  80
Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
                85                  90                  95
Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr
            100                 105                 110
Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu
        115                 120                 125
Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly
    130                 135                 140
Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr
145                 150                 155                 160
Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
 1               5                  10                  15
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln
            20                  25                  30
Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val
        35                  40                  45
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro
    50                  55                  60
Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr
65                  70                  75                  80
Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro
                85                  90                  95
Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe
            100                 105                 110
Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys
        115                 120                 125
Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser
    130                 135                 140
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
145                 150                 155                 160
Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp
 1               5                  10                  15
Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln
            20                  25                  30
Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu
        35                  40                  45
Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu
    50                  55                  60
Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr
65                  70                  75                  80
Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp
                85                  90                  95
Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg
            100                 105                 110
Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu
        115                 120                 125
Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala
    130                 135                 140
Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu
145                 150                 155                 160
Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr
 1               5                  10                  15
Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala
            20                  25                  30
Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg
        35                  40                  45
Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln
    50                  55                  60
Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu
65                  70                  75                  80
Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala
                85                  90                  95
Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys
            100                 105                 110
Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr
        115                 120                 125
Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro
    130                 135                 140
Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu
145                 150                 155                 160
Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys
 1               5                  10                  15
Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val
            20                  25                  30
Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
        35                  40                  45
Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu
    50                  55                  60
His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
65                  70                  75                  80
Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
                85                  90                  95
Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
            100                 105                 110
Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
        115                 120                 125
Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro
    130                 135                 140
Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
145                 150                 155                 160
Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val
 1               5                  10                  15
```

```
Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu
            20                  25                  30
Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
        35                  40                  45
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His
    50                  55                  60
Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
65                  70                  75                  80
Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
                85                  90                  95
Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
            100                 105                 110
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
        115                 120                 125
Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
    130                 135                 140
Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
145                 150                 155                 160
Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn
 1               5                  10                  15
Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val
            20                  25                  30
Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala
        35                  40                  45
Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val
    50                  55                  60
Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
65                  70                  75                  80
Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala
                85                  90                  95
Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg
            100                 105                 110
Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu
        115                 120                 125
Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu
    130                 135                 140
Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
145                 150                 155                 160
Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe
 1               5                  10                  15
Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
            20                  25                  30
Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
        35                  40                  45
Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
    50                  55                  60
Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
```

```
65                  70                  75                  80
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
                85                  90                  95
Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
            100                 105                 110
Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
        115                 120                 125
Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile
    130                 135                 140
Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala
145                 150                 155                 160
Glu Asn Ile Thr Thr Gly Cys Ala Glu His
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr
 1               5                  10                  15
Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln
            20                  25                  30
Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu
        35                  40                  45
Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys
    50                  55                  60
Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly
65                  70                  75                  80
Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro
                85                  90                  95
Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr
            100                 105                 110
Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys
        115                 120                 125
Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys
    130                 135                 140
Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
145                 150                 155                 160
Asn Ile Thr Thr Gly Cys Ala Glu His Cys
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala
 1               5                  10                  15
Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly
            20                  25                  30
Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val
        35                  40                  45
Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala
    50                  55                  60
Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala
65                  70                  75                  80
Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu
                85                  90                  95
Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser
            100                 105                 110
Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg
        115                 120                 125
```

```
Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
    130                 135                 140
Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
145                 150                 155                 160
Ile Thr Thr Gly Cys Ala Glu His Cys Ser
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
 1               5                  10                  15
Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
            20                  25                  30
Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn
        35                  40                  45
Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
    50                  55                  60
Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln
65                  70                  75                  80
Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
                85                  90                  95
Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
            100                 105                 110
Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
        115                 120                 125
Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
    130                 135                 140
Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
145                 150                 155                 160
Thr Thr Gly Cys Ala Glu His Cys Ser Leu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
 1               5                  10                  15
Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
            20                  25                  30
Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
        35                  40                  45
Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
    50                  55                  60
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
65                  70                  75                  80
Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr
                85                  90                  95
Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe
            100                 105                 110
Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly
        115                 120                 125
Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg
    130                 135                 140
Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
145                 150                 155                 160
Thr Gly Cys Ala Glu His Cys Ser Leu Asn
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
 1               5                  10                  15
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
            20                  25                  30
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
        35                  40                  45
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
    50                  55                  60
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
65                  70                  75                  80
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
                85                  90                  95
Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
            100                 105                 110
Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
        115                 120                 125
Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val
    130                 135                 140
Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr
145                 150                 155                 160
Gly Cys Ala Glu His Cys Ser Leu Asn Glu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
 1               5                  10                  15
Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
            20                  25                  30
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln
        35                  40                  45
Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
    50                  55                  60
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
65                  70                  75                  80
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
                85                  90                  95
Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
            100                 105                 110
Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg
        115                 120                 125
Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu
    130                 135                 140
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
145                 150                 155                 160
Cys Ala Glu His Cys Ser Leu Asn Glu Asn
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
 1               5                  10                  15
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
            20                  25                  30
Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
        35                  40                  45
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
    50                  55                  60
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
65                  70                  75                  80
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
                85                  90                  95
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
            100                 105                 110
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
        115                 120                 125
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
    130                 135                 140
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
145                 150                 155                 160
Glu His Cys Ser Leu Asn Glu Asn Ile Thr
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
 1               5                  10                  15
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
            20                  25                  30
Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu
        35                  40                  45
Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu
    50                  55                  60
Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
65                  70                  75                  80
Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr
                85                  90                  95
Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu
            100                 105                 110
Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly
        115                 120                 125
Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr
    130                 135                 140
Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu
145                 150                 155                 160
His Cys Ser Leu Asn Glu Asn Ile Thr Val
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln
 1               5                  10                  15
```

```
Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val
            20                  25                  30
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro
        35                  40                  45
Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr
    50                  55                  60
Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro
65                  70                  75                  80
Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe
                85                  90                  95
Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys
            100                 105                 110
Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser
        115                 120                 125
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
    130                 135                 140
Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
145                 150                 155                 160
Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
 1               5                  10                  15
Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
            20                  25                  30
Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
        35                  40                  45
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
    50                  55                  60
Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr
65                  70                  75                  80
Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe
                85                  90                  95
Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly
            100                 105                 110
Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg
        115                 120                 125
Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
    130                 135                 140
Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
145                 150                 155                 160
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
 1               5                  10                  15
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
            20                  25                  30
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
        35                  40                  45
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
    50                  55                  60
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
```

65 70 75 80
Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
85 90 95
Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
100 105 110
Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val
115 120 125
Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr
130 135 140
Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp
145 150 155 160
Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
165 170

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
1 5 10 15
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln
20 25 30
Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
35 40 45
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
50 55 60
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
65 70 75 80
Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
85 90 95
Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg
100 105 110
Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu
115 120 125
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
130 135 140
Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr
145 150 155 160
Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
165 170

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
1 5 10 15
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
20 25 30
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
35 40 45
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
50 55 60
Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala
65 70 75 80
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly
85 90 95
Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly
100 105 110
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu
115 120 125

```
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
    130                 135                 140
Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys
145                 150                 155                 160
Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu
 1               5                  10                  15
His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
            20                  25                  30
Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
        35                  40                  45
Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
    50                  55                  60
Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
65                  70                  75                  80
Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro
                85                  90                  95
Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
            100                 105                 110
Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu
        115                 120                 125
Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
    130                 135                 140
Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
145                 150                 155                 160
Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His
 1               5                  10                  15
Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
            20                  25                  30
Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
        35                  40                  45
Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
    50                  55                  60
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
65                  70                  75                  80
Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
                85                  90                  95
Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
            100                 105                 110
Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn
        115                 120                 125
Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
    130                 135                 140
Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
145                 150                 155                 160
Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val
 1               5                  10                  15
Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
            20                  25                  30
Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala
        35                  40                  45
Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg
    50                  55                  60
Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu
65                  70                  75                  80
Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu
                85                  90                  95
Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
            100                 105                 110
Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
        115                 120                 125
Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
    130                 135                 140
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
145                 150                 155                 160
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
 1               5                  10                  15
Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
            20                  25                  30
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
        35                  40                  45
Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
    50                  55                  60
Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
65                  70                  75                  80
Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile
                85                  90                  95
Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala
            100                 105                 110
Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn
        115                 120                 125
Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
    130                 135                 140
Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
145                 150                 155                 160
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys
 1               5                  10                  15
Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly
            20                  25                  30
Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro
        35                  40                  45
Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr
    50                  55                  60
Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys
65                  70                  75                  80
Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys
                85                  90                  95
Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
            100                 105                 110
Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
        115                 120                 125
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
    130                 135                 140
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
145                 150                 155                 160
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala
 1               5                  10                  15
Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala
            20                  25                  30
Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu
        35                  40                  45
Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser
    50                  55                  60
Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg
65                  70                  75                  80
Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
                85                  90                  95
Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
            100                 105                 110
Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
        115                 120                 125
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
    130                 135                 140
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
145                 150                 155                 160
Ala Val Leu Arg Gly Gln Ala Leu Leu Val
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
 1               5                  10                  15
```

```
Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln
            20                  25                  30
Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
        35                  40                  45
Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
    50                  55                  60
Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
65                  70                  75                  80
Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
                85                  90                  95
Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
            100                 105                 110
Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val
        115                 120                 125
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
    130                 135                 140
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
145                 150                 155                 160
Val Leu Arg Gly Gln Ala Leu Leu Val Asn
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
 1               5                  10                  15
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
            20                  25                  30
Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr
        35                  40                  45
Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe
    50                  55                  60
Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly
65                  70                  75                  80
Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg
                85                  90                  95
Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
            100                 105                 110
Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
        115                 120                 125
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln
    130                 135                 140
Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val
145                 150                 155                 160
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
 1               5                  10                  15
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
            20                  25                  30
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
        35                  40                  45
Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
    50                  55                  60
Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
```

60

65 70 75 80
Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val
85 90 95
Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr
100 105 110
Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp
115 120 125
Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln
130 135 140
Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu
145 150 155 160
Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
165 170

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
1 5 10 15
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
20 25 30
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
35 40 45
Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
50 55 60
Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg
65 70 75 80
Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu
85 90 95
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
100 105 110
Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr
115 120 125
Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala
130 135 140
Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg
145 150 155 160
Gly Gln Ala Leu Leu Val Asn Ser Ser Gln
165 170

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
1 5 10 15
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
20 25 30
Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala
35 40 45
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly
50 55 60
Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly
65 70 75 80
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu
85 90 95
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
100 105 110
Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys
115 120 125

```
Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val
    130                 135                 140
Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
145                 150                 155                 160
Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
 1               5                  10                  15
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
            20                  25                  30
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
        35                  40                  45
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
    50                  55                  60
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
65                  70                  75                  80
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
                85                  90                  95
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
            100                 105                 110
Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val
        115                 120                 125
Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu
    130                 135                 140
Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
145                 150                 155                 160
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```
Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala
 1               5                  10                  15
Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys
            20                  25                  30
Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr
        35                  40                  45
Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro
    50                  55                  60
Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu
65                  70                  75                  80
Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser
                85                  90                  95
Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala
            100                 105                 110
Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly
        115                 120                 125
Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val
    130                 135                 140
Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala
145                 150                 155                 160
Val Ser Gly Leu Arg Ser Leu Thr Thr Leu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
 1               5                  10                  15
Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
            20                  25                  30
Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
        35                  40                  45
Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro
    50                  55                  60
Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
65                  70                  75                  80
Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu
                85                  90                  95
Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
            100                 105                 110
Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
        115                 120                 125
Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn
    130                 135                 140
Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
145                 150                 155                 160
Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

```
Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
 1               5                  10                  15
Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
            20                  25                  30
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
        35                  40                  45
Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
    50                  55                  60
Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
65                  70                  75                  80
Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn
                85                  90                  95
Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
            100                 105                 110
Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
        115                 120                 125
Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
    130                 135                 140
Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
145                 150                 155                 160
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```
Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala
 1               5                  10                  15
Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg
            20                  25                  30
Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu
        35                  40                  45
Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu
    50                  55                  60
Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
65                  70                  75                  80
Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
                85                  90                  95
Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
            100                 105                 110
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
        115                 120                 125
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
    130                 135                 140
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
145                 150                 155                 160
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

```
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
 1               5                  10                  15
Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
            20                  25                  30
Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
        35                  40                  45
Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile
    50                  55                  60
Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala
65                  70                  75                  80
Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn
                85                  90                  95
Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
            100                 105                 110
Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
        115                 120                 125
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln
    130                 135                 140
Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
145                 150                 155                 160
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

```
Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro
 1               5                  10                  15
```

```
Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr
            20                  25                  30
Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys
        35                  40                  45
Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys
    50                  55                  60
Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
65                  70                  75                  80
Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
                85                  90                  95
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
            100                 105                 110
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
        115                 120                 125
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
    130                 135                 140
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
145                 150                 155                 160
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```
Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu
 1               5                  10                  15
Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser
            20                  25                  30
Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg
        35                  40                  45
Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
    50                  55                  60
Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
65                  70                  75                  80
Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
                85                  90                  95
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
            100                 105                 110
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
        115                 120                 125
Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
    130                 135                 140
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
145                 150                 155                 160
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

```
Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
 1               5                  10                  15
Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
            20                  25                  30
Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
        35                  40                  45
Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
    50                  55                  60
Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
```

```
65                  70                  75                  80
Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val
                85                  90                  95
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
            100                 105                 110
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
        115                 120                 125
Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu
    130                 135                 140
Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu
145                 150                 155                 160
Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

```
Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr
 1               5                  10                  15
Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe
            20                  25                  30
Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly
        35                  40                  45
Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg
    50                  55                  60
Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
65                  70                  75                  80
Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
                85                  90                  95
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln
            100                 105                 110
Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val
        115                 120                 125
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro
    130                 135                 140
Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr
145                 150                 155                 160
Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
 1               5                  10                  15
Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
            20                  25                  30
Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
        35                  40                  45
Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val
    50                  55                  60
Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr
65                  70                  75                  80
Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp
                85                  90                  95
Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln
            100                 105                 110
Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu
        115                 120                 125
```

```
Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu
    130                 135                 140
Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr
145                 150                 155                 160
Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
 1               5                  10                  15
Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
            20                  25                  30
Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg
        35                  40                  45
Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu
    50                  55                  60
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
65                  70                  75                  80
Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr
                85                  90                  95
Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala
            100                 105                 110
Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg
        115                 120                 125
Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln
    130                 135                 140
Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu
145                 150                 155                 160
Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```
Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala
 1               5                  10                  15
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly
            20                  25                  30
Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly
        35                  40                  45
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu
    50                  55                  60
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
65                  70                  75                  80
Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys
                85                  90                  95
Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val
            100                 105                 110
Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
        115                 120                 125
Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu
    130                 135                 140
His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
145                 150                 155                 160
Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
 1               5                  10                  15
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
            20                  25                  30
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
        35                  40                  45
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
    50                  55                  60
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
65                  70                  75                  80
Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val
                85                  90                  95
Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu
            100                 105                 110
Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
        115                 120                 125
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His
    130                 135                 140
Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
145                 150                 155                 160
Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr
 1               5                  10                  15
Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu
            20                  25                  30
Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly
        35                  40                  45
Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr
    50                  55                  60
Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu
65                  70                  75                  80
His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn
                85                  90                  95
Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val
            100                 105                 110
Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala
        115                 120                 125
Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val
    130                 135                 140
Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
145                 150                 155                 160
Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```
Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe
 1               5                  10                  15
Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys
            20                  25                  30
Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser
        35                  40                  45
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
    50                  55                  60
Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
65                  70                  75                  80
Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe
                85                  90                  95
Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
            100                 105                 110
Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
        115                 120                 125
Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
    130                 135                 140
Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
145                 150                 155                 160
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```
Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg
 1               5                  10                  15
Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu
            20                  25                  30
Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala
        35                  40                  45
Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu
    50                  55                  60
Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys
65                  70                  75                  80
Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr
                85                  90                  95
Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln
            100                 105                 110
Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu
        115                 120                 125
Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys
    130                 135                 140
Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly
145                 150                 155                 160
Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```
Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys
 1               5                  10                  15
```

```
Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr
            20                  25                  30
Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro
        35                  40                  45
Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu
    50                  55                  60
Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser
65                  70                  75                  80
Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala
                85                  90                  95
Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly
            100                 105                 110
Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val
        115                 120                 125
Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala
    130                 135                 140
Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala
145                 150                 155                 160
Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```
Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
 1               5                  10                  15
Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
            20                  25                  30
Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro
        35                  40                  45
Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
    50                  55                  60
Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu
65                  70                  75                  80
Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
                85                  90                  95
Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
            100                 105                 110
Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn
        115                 120                 125
Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
    130                 135                 140
Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln
145                 150                 155                 160
Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

```
Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
 1               5                  10                  15
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
            20                  25                  30
Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
        35                  40                  45
Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
    50                  55                  60
Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn
```

70

65 70 75 80
Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
85 90 95
Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
100 105 110
Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
115 120 125
Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
130 135 140
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
145 150 155 160
Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
165 170

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg
1 5 10 15
Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu
20 25 30
Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu
35 40 45
Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
50 55 60
Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
65 70 75 80
Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
85 90 95
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
100 105 110
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
115 120 125
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
130 135 140
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
145 150 155 160
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala
165 170

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
1 5 10 15
Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
20 25 30
Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile
35 40 45
Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala
50 55 60
Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn
65 70 75 80
Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
85 90 95
Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
100 105 110
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln
115 120 125

```
Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
    130                 135                 140
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
145                 150                 155                 160
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```
Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr
 1               5                  10                  15
Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys
            20                  25                  30
Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys
        35                  40                  45
Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
    50                  55                  60
Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
65                  70                  75                  80
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
                85                  90                  95
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
            100                 105                 110
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
        115                 120                 125
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
    130                 135                 140
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Ala Lys Glu Ala
145                 150                 155                 160
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

```
Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser
 1               5                  10                  15
Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg
            20                  25                  30
Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
        35                  40                  45
Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
    50                  55                  60
Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
65                  70                  75                  80
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
                85                  90                  95
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
            100                 105                 110
Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
        115                 120                 125
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
    130                 135                 140
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
145                 150                 155                 160
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

```
Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
 1               5                  10                  15
Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
            20                  25                  30
Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
        35                  40                  45
Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
    50                  55                  60
Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val
65                  70                  75                  80
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
                85                  90                  95
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
            100                 105                 110
Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu
        115                 120                 125
Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu
    130                 135                 140
Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
145                 150                 155                 160
Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

```
AATATCACGA CGGGCTGTGC TGAACACTGC AGCTTGAATG AGAATATCAC TGTCCCAGAC     60
ACCAAAGTTA ATTTCTATGC CTGGAAGAGG ATGGAGGTCG GGCAGCAGGC CGTAGAAGTC    120
TGGCAGGGCC TGGCCCTGCT GTCGGAAGCT GTCCTGCGGG GCCAGGCCCT GTTGGTCAAC    180
TCTTCCCAGC CGTGGGAGCC CCTGCAGCTG CATGTGGATA AAGCCGTCAG TGGCCTTCGC    240
AGCCTCACCA CTCTGCTTCG GGCTCTGGGA GCCCAGAAGG AAGCCATCTC CCCTCCAGAT    300
GCGGCCTCAG CTGCTCCACT CCGAACAATC ACTGCTGACA CTTTCCGCAA ACTCTTCCGA    360
GTCTACTCCA ATTTCCTCCG GGGAAAGCTG AAGCTGTACA CAGGGGAGGC CTGCAGGACA    420
GGGGACAGAT GAGGCGGCGG CTCCCCCCAC CACGCCTCAT CTGTGACAGC CGAGTCCTGG    480
AGAGGTACCT CTTGGAGGCC AAGGAGGCCG AG                                  512
```

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

```
ATCACGACGG GCTGTGCTGA ACACTGCAGC TTGAATGAGA ATATCACTGT CCCAGACACC     60
AAAGTTAATT TCTATGCCTG GAAGAGGATG GAGGTCGGGC AGCAGGCCGT AGAAGTCTGG    120
CAGGGCCTGG CCCTGCTGTC GGAAGCTGTC CTGCGGGGCC AGGCCCTGTT GGTCAACTCT    180
TCCCAGCCGT GGGAGCCCCT GCAGCTGCAT GTGGATAAAG CCGTCAGTGG CCTTCGCAGC    240
CTCACCACTC TGCTTCGGGC TCTGGGAGCC CAGAAGGAAG CCATCTCCCC TCCAGATGCG    300
GCCTCAGCTG CTCCACTCCG AACAATCACT GCTGACACTT TCCGCAAACT CTTCCGAGTC    360
TACTCCAATT TCCTCCGGGG AAAGCTGAAG CTGTACACAG GGGAGGCCTG CAGGACAGGG    420
GACAGATGAG GCGGCGGCTC CCCCCACCAC GCCTCATCTG TGACAGCCGA GTCCTGGAGA    480
GGTACCTCTT GGAGGCCAAG GAGGCCGAGA AT                                  512
```

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

ACGACGGGCT GTGCTGAACA CTGCAGCTTG AATGAGAATA TCACTGTCCC AGACACCAAA 60
GTTAATTTCT ATGCCTGGAA GAGGATGGAG GTCGGGCAGC AGGCCGTAGA AGTCTGGCAG 120
GGCCTGGCCC TGCTGTCGGA AGCTGTCCTG CGGGGCCAGG CCCTGTTGGT CAACTCTTCC 180
CAGCCGTGGG AGCCCCTGCA GCTGCATGTG GATAAAGCCG TCAGTGGCCT TCGCAGCCTC 240
ACCACTCTGC TTCGGGCTCT GGGAGCCCAG AAGGAAGCCA TCTCCCCTCC AGATGCGGCC 300
TCAGCTGCTC CACTCCGAAC AATCACTGCT GACACTTTCC GCAAACTCTT CCGAGTCTAC 360
TCCAATTTCC TCCGGGGAAA GCTGAAGCTG TACACAGGGG AGGCCTGCAG GACAGGGGAC 420
AGATGAGGCG GCGGCTCCCC CCACCACGCC TCATCTGTGA CAGCCGAGTC CTGGAGAGGT 480
ACCTCTTGGA GGCCAAGGAG GCCGAGAATA TC 512

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

ACGGGCTGTG CTGAACACTG CAGCTTGAAT GAGAATATCA CTGTCCCAGA CACCAAAGTT 60
AATTTCTATG CCTGGAAGAG GATGGAGGTC GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC 120
CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG GGCCAGGCCC TGTTGGTCAA CTCTTCCCAG 180
CCGTGGGAGC CCCTGCAGCT GCATGTGGAT AAAGCCGTCA GTGGCCTTCG CAGCCTCACC 240
ACTCTGCTTC GGGCTCTGGG AGCCCAGAAG GAAGCCATCT CCCCTCCAGA TGCGGCCTCA 300
GCTGCTCCAC TCCGAACAAT CACTGCTGAC ACTTTCCGCA AACTCTTCCG AGTCTACTCC 360
AATTTCCTCC GGGGAAAGCT GAAGCTGTAC ACAGGGGAGG CCTGCAGGAC AGGGGACAGA 420
TGAGGCGGCG GCTCCCCCCA CCACGCCTCA TCTGTGACAG CCGAGTCCTG GAGAGGTACC 480
TCTTGGAGGC CAAGGAGGCC GAGAATATCA CG 512

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GGCTGTGCTG AACACTGCAG CTTGAATGAG AATATCACTG TCCCAGACAC CAAAGTTAAT 60
TTCTATGCCT GGAAGAGGAT GGAGGTCGGG CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG 120
GCCCTGCTGT CGGAAGCTGT CCTGCGGGGC CAGGCCCTGT TGGTCAACTC TTCCCAGCCG 180
TGGGAGCCCC TGCAGCTGCA TGTGGATAAA GCCGTCAGTG GCCTTCGCAG CCTCACCACT 240
CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA GCCATCTCCC CTCCAGATGC GGCCTCAGCT 300
GCTCCACTCC GAACAATCAC TGCTGACACT TTCCGCAAAC TCTTCCGAGT CTACTCCAAT 360
TTCCTCCGGG GAAAGCTGAA GCTGTACACA GGGGAGGCCT GCAGGACAGG GGACAGATGA 420
GGCGGCGGCT CCCCCCACCA CGCCTCATCT GTGACAGCCG AGTCCTGGAG AGGTACCTCT 480
TGGAGGCCAA GGAGGCCGAG AATATCACGA CG 512

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

TGTGCTGAAC ACTGCAGCTT GAATGAGAAT ATCACTGTCC CAGACACCAA AGTTAATTTC 60
TATGCCTGGA AGAGGATGGA GGTCGGGCAG CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC 120
CTGCTGTCGG AAGCTGTCCT GCGGGGCCAG GCCCTGTTGG TCAACTCTTC CCAGCCGTGG 180

GAGCCCCTGC AGCTGCATGT GGATAAAGCC GTCAGTGGCC TTCGCAGCCT CACCACTCTG 240
CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC ATCTCCCCTC CAGATGCGGC CTCAGCTGCT 300
CCACTCCGAA CAATCACTGC TGACACTTTC CGCAAACTCT TCCGAGTCTA CTCCAATTTC 360
CTCCGGGGAA AGCTGAAGCT GTACACAGGG GAGGCCTGCA GGACAGGGGA CAGATGAGGC 420
GGCGGCTCCC CCCACCACGC CTCATCTGTG ACAGCCGAGT CCTGGAGAGG TACCTCTTGG 480
AGGCCAAGGA GGCCGAGAAT ATCACGACGG GC 512

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GCTGAACACT GCAGCTTGAA TGAGAATATC ACTGTCCCAG ACACCAAAGT TAATTTCTAT 60
GCCTGGAAGA GGATGGAGGT CGGGCAGCAG GCCGTAGAAG TCTGGCAGGG CCTGGCCCTG 120
CTGTCGGAAG CTGTCCTGCG GGGCCAGGCC CTGTTGGTCA ACTCTTCCCA GCCGTGGGAG 180
CCCCTGCAGC TGCATGTGGA TAAAGCCGTC AGTGGCCTTC GCAGCCTCAC CACTCTGCTT 240
CGGGCTCTGG GAGCCCAGAA GGAAGCCATC TCCCCTCCAG ATGCGGCCTC AGCTGCTCCA 300
CTCCGAACAA TCACTGCTGA CACTTTCCGC AAACTCTTCC GAGTCTACTC CAATTTCCTC 360
CGGGGAAAGC TGAAGCTGTA CACAGGGGAG GCCTGCAGGA CAGGGGACAG ATGAGGCGGC 420
GGCTCCCCCC ACCACGCCTC ATCTGTGACA GCCGAGTCCT GGAGAGGTAC CTCTTGGAGG 480
CCAAGGAGGC CGAGAATATC ACGACGGGCT GT 512

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GAACACTGCA GCTTGAATGA GAATATCACT GTCCCAGACA CCAAAGTTAA TTTCTATGCC 60
TGGAAGAGGA TGGAGGTCGG GCAGCAGGCC GTAGAAGTCT GGCAGGGCCT GGCCCTGCTG 120
TCGGAAGCTG TCCTGCGGGG CCAGGCCCTG TTGGTCAACT CTTCCCAGCC GTGGGAGCCC 180
CTGCAGCTGC ATGTGGATAA AGCCGTCAGT GGCCTTCGCA GCCTCACCAC TCTGCTTCGG 240
GCTCTGGGAG CCCAGAAGGA AGCCATCTCC CCTCCAGATG CGGCCTCAGC TGCTCCACTC 300
CGAACAATCA CTGCTGACAC TTTCCGCAAA CTCTTCCGAG TCTACTCCAA TTTCCTCCGG 360
GGAAAGCTGA AGCTGTACAC AGGGGAGGCC TGCAGGACAG GGGACAGATG AGGCGGCGGC 420
TCCCCCCACC ACGCCTCATC TGTGACAGCC GAGTCCTGGA GAGGTACCTC TTGGAGGCCA 480
AGGAGGCCGA GAATATCACG ACGGGCTGTG CT 512

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

CACTGCAGCT TGAATGAGAA TATCACTGTC CCAGACACCA AAGTTAATTT CTATGCCTGG 60
AAGAGGATGG AGGTCGGGCA GCAGGCCGTA GAAGTCTGGC AGGGCCTGGC CCTGCTGTCG 120
GAAGCTGTCC TGCGGGGCCA GGCCCTGTTG GTCAACTCTT CCCAGCCGTG GGAGCCCCTG 180
CAGCTGCATG TGGATAAAGC CGTCAGTGGC CTTCGCAGCC TCACCACTCT GCTTCGGGCT 240
CTGGGAGCCC AGAAGGAAGC CATCTCCCCT CCAGATGCGG CCTCAGCTGC TCCACTCCGA 300
ACAATCACTG CTGACACTTT CCGCAAACTC TTCCGAGTCT ACTCCAATTT CCTCCGGGGA 360
AAGCTGAAGC TGTACACAGG GGAGGCCTGC AGGACAGGGG ACAGATGAGG CGGCGGCTCC 420
CCCCACCACG CCTCATCTGT GACAGCCGAG TCCTGGAGAG GTACCTCTTG GAGGCCAAGG 480
AGGCCGAGAA TATCACGACG GGCTGTGCTG AA 512

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```
TGCAGCTTGA ATGAGAATAT CACTGTCCCA GACACCAAAG TTAATTTCTA TGCCTGGAAG     60
AGGATGGAGG TCGGGCAGCA GGCCGTAGAA GTCTGGCAGG GCCTGGCCCT GCTGTCGGAA    120
GCTGTCCTGC GGGGCCAGGC CCTGTTGGTC AACTCTTCCC AGCCGTGGGA GCCCCTGCAG    180
CTGCATGTGG ATAAAGCCGT CAGTGGCCTT CGCAGCCTCA CCACTCTGCT TCGGGCTCTG    240
GGAGCCCAGA AGGAAGCCAT CTCCCCTCCA GATGCGGCCT CAGCTGCTCC ACTCCGAACA    300
ATCACTGCTG ACACTTTCCG CAAACTCTTC CGAGTCTACT CCAATTTCCT CCGGGGAAAG    360
CTGAAGCTGT ACACAGGGGA GGCCTGCAGG ACAGGGGACA GATGAGGCGG CGGCTCCCCC    420
CACCACGCCT CATCTGTGAC AGCCGAGTCC TGGAGAGGTA CCTCTTGGAG GCCAAGGAGG    480
CCGAGAATAT CACGACGGGC TGTGCTGAAC AC                                   512
```

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

```
AGCTTGAATG AGAATATCAC TGTCCCAGAC ACCAAAGTTA ATTTCTATGC CTGGAAGAGG     60
ATGGAGGTCG GGCAGCAGGC CGTAGAAGTC TGGCAGGGCC TGGCCCTGCT GTCGGAAGCT    120
GTCCTGCGGG GCCAGGCCCT GTTGGTCAAC TCTTCCCAGC CGTGGGAGCC CCTGCAGCTG    180
CATGTGGATA AAGCCGTCAG TGGCCTTCGC AGCCTCACCA CTCTGCTTCG GGCTCTGGGA    240
GCCCAGAAGG AAGCCATCTC CCCTCCAGAT GCGGCCTCAG CTGCTCCACT CCGAACAATC    300
ACTGCTGACA CTTTCCGCAA ACTCTTCCGA GTCTACTCCA ATTTCCTCCG GGGAAAGCTG    360
AAGCTGTACA CAGGGGAGGC CTGCAGGACA GGGGACAGAT GAGGCGGCGG CTCCCCCCAC    420
CACGCCTCAT CTGTGACAGC CGAGTCCTGG AGAGGTACCT CTTGGAGGCC AAGGAGGCCG    480
AGAATATCAC GACGGGCTGT GCTGAACACT GC                                   512
```

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

```
TTGAATGAGA ATATCACTGT CCCAGACACC AAAGTTAATT TCTATGCCTG GAAGAGGATG     60
GAGGTCGGGC AGCAGGCCGT AGAAGTCTGG CAGGGCCTGG CCCTGCTGTC GGAAGCTGTC    120
CTGCGGGGCC AGGCCCTGTT GGTCAACTCT TCCCAGCCGT GGGAGCCCCT GCAGCTGCAT    180
GTGGATAAAG CCGTCAGTGG CCTTCGCAGC CTCACCACTC TGCTTCGGGC TCTGGGAGCC    240
CAGAAGGAAG CCATCTCCCC TCCAGATGCG GCCTCAGCTG CTCCACTCCG AACAATCACT    300
GCTGACACTT TCCGCAAACT CTTCCGAGTC TACTCCAATT TCCTCCGGGG AAAGCTGAAG    360
CTGTACACAG GGGAGGCCTG CAGGACAGGG GACAGATGAG GCGGCGGCTC CCCCCACCAC    420
GCCTCATCTG TGACAGCCGA GTCCTGGAGA GGTACCTCTT GGAGGCCAAG GAGGCCGAGA    480
ATATCACGAC GGGCTGTGCT GAACACTGCA GC                                   512
```

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
AATGAGAATA TCACTGTCCC AGACACCAAA GTTAATTTCT ATGCCTGGAA GAGGATGGAG     60
GTCGGGCAGC AGGCCGTAGA AGTCTGGCAG GGCCTGGCCC TGCTGTCGGA AGCTGTCCTG    120
CGGGGCCAGG CCCTGTTGGT CAACTCTTCC CAGCCGTGGG AGCCCCTGCA GCTGCATGTG    180
GATAAAGCCG TCAGTGGCCT TCGCAGCCTC ACCACTCTGC TTCGGGCTCT GGGAGCCCAG    240
AAGGAAGCCA TCTCCCCTCC AGATGCGGCC TCAGCTGCTC CACTCCGAAC AATCACTGCT    300
GACACTTTCC GCAAACTCTT CCGAGTCTAC TCCAATTTCC TCCGGGGAAA GCTGAAGCTG    360
TACACAGGGG AGGCCTGCAG GACAGGGGAC AGATGAGGCG GCGGCTCCCC CCACCACGCC    420
TCATCTGTGA CAGCCGAGTC CTGGAGAGGT ACCTCTTGGA GGCCAAGGAG GCCGAGAATA    480
TCACGACGGG CTGTGCTGAA CACTGCAGCT TG                                   512
```

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

GAGAATATCA CTGTCCCAGA CACCAAAGTT AATTTCTATG CCTGGAAGAG GATGGAGGTC 60
GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG 120
GGCCAGGCCC TGTTGGTCAA CTCTTCCCAG CCGTGGGAGC CCCTGCAGCT GCATGTGGAT 180
AAAGCCGTCA GTGGCCTTCG CAGCCTCACC ACTCTGCTTC GGGCTCTGGG AGCCCAGAAG 240
GAAGCCATCT CCCCTCCAGA TGCGGCCTCA GCTGCTCCAC TCCGAACAAT CACTGCTGAC 300
ACTTTCCGCA AACTCTTCCG AGTCTACTCC AATTTCCTCC GGGGAAAGCT GAAGCTGTAC 360
ACAGGGGAGG CCTGCAGGAC AGGGGACAGA TGAGGCGGCG GCTCCCCCCA CCACGCCTCA 420
TCTGTGACAG CCGAGTCCTG GAGAGGTACC TCTTGGAGGC CAAGGAGGCC GAGAATATCA 480
CGACGGGCTG TGCTGAACAC TGCAGCTTGA AT 512

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

AATATCACTG TCCCAGACAC CAAAGTTAAT TTCTATGCCT GGAAGAGGAT GGAGGTCGGG 60
CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG GCCCTGCTGT CGGAAGCTGT CCTGCGGGGC 120
CAGGCCCTGT TGGTCAACTC TTCCCAGCCG TGGGAGCCCC TGCAGCTGCA TGTGGATAAA 180
GCCGTCAGTG GCCTTCGCAG CCTCACCACT CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA 240
GCCATCTCCC CTCCAGATGC GGCCTCAGCT GCTCCACTCC GAACAATCAC TGCTGACACT 300
TTCCGCAAAC TCTTCCGAGT CTACTCCAAT TTCCTCCGGG GAAAGCTGAA GCTGTACACA 360
GGGGAGGCCT GCAGGACAGG GGACAGATGA GGCGGCGGCT CCCCCCACCA CGCCTCATCT 420
GTGACAGCCG AGTCCTGGAG AGGTACCTCT TGGAGGCCAA GGAGGCCGAG AATATCACGA 480
CGGGCTGTGC TGAACACTGC AGCTTGAATG AG 512

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

ATCACTGTCC CAGACACCAA AGTTAATTTC TATGCCTGGA AGAGGATGGA GGTCGGGCAG 60
CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC CTGCTGTCGG AAGCTGTCCT GCGGGGCCAG 120
GCCCTGTTGG TCAACTCTTC CCAGCCGTGG GAGCCCCTGC AGCTGCATGT GGATAAAGCC 180
GTCAGTGGCC TTCGCAGCCT CACCACTCTG CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC 240
ATCTCCCCTC CAGATGCGGC CTCAGCTGCT CCACTCCGAA CAATCACTGC TGACACTTTC 300
CGCAAACTCT TCCGAGTCTA CTCCAATTTC CTCCGGGGAA AGCTGAAGCT GTACACAGGG 360
GAGGCCTGCA GGACAGGGGA CAGATGAGGC GGCGGCTCCC CCCACCACGC CTCATCTGTG 420
ACAGCCGAGT CCTGGAGAGG TACCTCTTGG AGGCCAAGGA GGCCGAGAAT ATCACGACGG 480
GCTGTGCTGA ACACTGCAGC TTGAATGAGA AT 512

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

ACTGTCCCAG ACACCAAAGT TAATTTCTAT GCCTGGAAGA GGATGGAGGT CGGGCAGCAG 60
GCCGTAGAAG TCTGGCAGGG CCTGGCCCTG CTGTCGGAAG CTGTCCTGCG GGGCCAGGCC 120
CTGTTGGTCA ACTCTTCCCA GCCGTGGGAG CCCCTGCAGC TGCATGTGGA TAAAGCCGTC 180

AGTGGCCTTC GCAGCCTCAC CACTCTGCTT CGGGCTCTGG GAGCCCAGAA GGAAGCCATC 240
TCCCCTCCAG ATGCGGCCTC AGCTGCTCCA CTCCGAACAA TCACTGCTGA CACTTTCCGC 300
AAACTCTTCC GAGTCTACTC CAATTTCCTC CGGGGAAAGC TGAAGCTGTA CACAGGGGAG 360
GCCTGCAGGA CAGGGGACAG ATGAGGCGGC GGCTCCCCCC ACCACGCCTC ATCTGTGACA 420
GCCGAGTCCT GGAGAGGTAC CTCTTGGAGG CCAAGGAGGC CGAGAATATC ACGACGGGCT 480
GTGCTGAACA CTGCAGCTTG AATGAGAATA ATC 513

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

GTCCCAGACA CCAAAGTTAA TTTCTATGCC TGGAAGAGGA TGGAGGTCGG GCAGCAGGCC 60
GTAGAAGTCT GGCAGGGCCT GGCCCTGCTG TCGGAAGCTG TCCTGCGGGG CCAGGCCCTG 120
TTGGTCAACT CTTCCCAGCC GTGGGAGCCC CTGCAGCTGC ATGTGGATAA AGCCGTCAGT 180
GGCCTTCGCA GCCTCACCAC TCTGCTTCGG GCTCTGGGAG CCCAGAAGGA AGCCATCTCC 240
CCTCCAGATG CGGCCTCAGC TGCTCCACTC CGAACAATCA CTGCTGACAC TTTCCGCAAA 300
CTCTTCCGAG TCTACTCCAA TTTCCTCCGG GGAAAGCTGA AGCTGTACAC AGGGGAGGCC 360
TGCAGGACAG GGGACAGATG AGGCGGCGGC TCCCCCCACC ACGCCTCATC TGTGACAGCC 420
GAGTCCTGGA GAGGTACCTC TTGGAGGCCA AGGAGGCCGA GAATATCACG ACGGGCTGTG 480
CTGAACACTG CAGCTTGAAT GAGAATAATC ACT 513

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

CCAGACACCA AAGTTAATTT CTATGCCTGG AAGAGGATGG AGGTCGGGCA GCAGGCCGTA 60
GAAGTCTGGC AGGGCCTGGC CCTGCTGTCG GAAGCTGTCC TGCGGGGCCA GGCCCTGTTG 120
GTCAACTCTT CCCAGCCGTG GGAGCCCCTG CAGCTGCATG TGGATAAAGC CGTCAGTGGC 180
CTTCGCAGCC TCACCACTCT GCTTCGGGCT CTGGGAGCCC AGAAGGAAGC CATCTCCCCT 240
CCAGATGCGG CCTCAGCTGC TCCACTCCGA ACAATCACTG CTGACACTTT CCGCAAACTC 300
TTCCGAGTCT ACTCCAATTT CCTCCGGGGA AAGCTGAAGC TGTACACAGG GGAGGCCTGC 360
AGGACAGGGG ACAGATGAGG CGGCGGCTCC CCCCACCACG CCTCATCTGT GACAGCCGAG 420
TCCTGGAGAG GTACCTCTTG GAGGCCAAGG AGGCCGAGAA TATCACGACG GGCTGTGCTG 480
AACACTGCAG CTTGAATGAG AATAATCACT GTC 513

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GACACCAAAG TTAATTTCTA TGCCTGGAAG AGGATGGAGG TCGGGCAGCA GGCCGTAGAA 60
GTCTGGCAGG GCCTGGCCCT GCTGTCGGAA GCTGTCCTGC GGGGCCAGGC CCTGTTGGTC 120
AACTCTTCCC AGCCGTGGGA GCCCCTGCAG CTGCATGTGG ATAAAGCCGT CAGTGGCCTT 180
CGCAGCCTCA CCACTCTGCT TCGGGCTCTG GGAGCCCAGA AGGAAGCCAT CTCCCCTCCA 240
GATGCGGCCT CAGCTGCTCC ACTCCGAACA ATCACTGCTG ACACTTTCCG CAAACTCTTC 300
CGAGTCTACT CCAATTTCCT CCGGGGAAAG CTGAAGCTGT ACACAGGGGA GGCCTGCAGG 360
ACAGGGGACA GATGAGGCGG CGGCTCCCCC CACCACGCCT CATCTGTGAC AGCCGAGTCC 420
TGGAGAGGTA CCTCTTGGAG GCCAAGGAGG CCGAGAATAT CACGACGGGC TGTGCTGAAC 480
ACTGCAGCTT GAATGAGAAT AATCACTGTC CCA 513

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
AGGATGGAGG TCGGGCAGCA GGCCGTAGAA GTCTGGCAGG GCCTGGCCCT GCTGTCGGAA     60
GCTGTCCTGC GGGGCCAGGC CCTGTTGGTC AACTCTTCCC AGCCGTGGGA GCCCCTGCAG    120
CTGCATGTGG ATAAAGCCGT CAGTGGCCTT CGCAGCCTCA CCACTCTGCT TCGGGCTCTG    180
GGAGCCCAGA AGGAAGCCAT CTCCCCTCCA GATGCGGCCT CAGCTGCTCC ACTCCGAACA    240
ATCACTGCTG ACACTTTCCG CAAACTCTTC CGAGTCTACT CCAATTTCCT CCGGGGAAAG    300
CTGAAGCTGT ACACAGGGGA GGCCTGCAGG ACAGGGGACA GATGAGGCGG CGGCTCCCCC    360
CACCACGCCT CATCTGTGAC AGCCGAGTCC TGGAGAGGTA CCTCTTGGAG GCCAAGGAGG    420
CCGAGAATAT CACGACGGGC TGTGCTGAAC ACTGCAGCTT GAATGAGAAT AATCACTGTC    480
CCAGACACCA AAGTTAATTT CTATGCCTGG AAG                                 513
```

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
ATGGAGGTCG GGCAGCAGGC CGTAGAAGTC TGGCAGGGCC TGGCCCTGCT GTCGGAAGCT     60
GTCCTGCGGG GCCAGGCCCT GTTGGTCAAC TCTTCCCAGC CGTGGGAGCC CCTGCAGCTG    120
CATGTGGATA AAGCCGTCAG TGGCCTTCGC AGCCTCACCA CTCTGCTTCG GGCTCTGGGA    180
GCCCAGAAGG AAGCCATCTC CCCTCCAGAT GCGGCCTCAG CTGCTCCACT CCGAACAATC    240
ACTGCTGACA CTTTCCGCAA ACTCTTCCGA GTCTACTCCA ATTTCCTCCG GGGAAAGCTG    300
AAGCTGTACA CAGGGGAGGC CTGCAGGACA GGGGACAGAT GAGGCGGCGG CTCCCCCCAC    360
CACGCCTCAT CTGTGACAGC CGAGTCCTGG AGAGGTACCT CTTGGAGGCC AAGGAGGCCG    420
AGAATATCAC GACGGGCTGT GCTGAACACT GCAGCTTGAA TGAGAATAAT CACTGTCCCA    480
GACACCAAAG TTAATTTCTA TGCCTGGAAG AGG                                 513
```

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
GAGGTCGGGC AGCAGGCCGT AGAAGTCTGG CAGGGCCTGG CCCTGCTGTC GGAAGCTGTC     60
CTGCGGGGCC AGGCCCTGTT GGTCAACTCT TCCCAGCCGT GGGAGCCCCT GCAGCTGCAT    120
GTGGATAAAG CCGTCAGTGG CCTTCGCAGC CTCACCACTC TGCTTCGGGC TCTGGGAGCC    180
CAGAAGGAAG CCATCTCCCC TCCAGATGCG GCCTCAGCTG CTCCACTCCG AACAATCACT    240
GCTGACACTT TCCGCAAACT CTTCCGAGTC TACTCCAATT TCCTCCGGGG AAAGCTGAAG    300
CTGTACACAG GGGAGGCCTG CAGGACAGGG GACAGATGAG GCGGCGGCTC CCCCCACCAC    360
GCCTCATCTG TGACAGCCGA GTCCTGGAGA GGTACCTCTT GGAGGCCAAG GAGGCCGAGA    420
ATATCACGAC GGGCTGTGCT GAACACTGCA GCTTGAATGA GAATAATCAC TGTCCCAGAC    480
ACCAAAGTTA ATTTCTATGC CTGGAAGAGG ATG                                 513
```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
GTCGGGCAGC AGGCCGTAGA AGTCTGGCAG GGCCTGGCCC TGCTGTCGGA AGCTGTCCTG     60
CGGGGCCAGG CCCTGTTGGT CAACTCTTCC CAGCCGTGGG AGCCCCTGCA GCTGCATGTG    120
GATAAAGCCG TCAGTGGCCT TCGCAGCCTC ACCACTCTGC TTCGGGCTCT GGGAGCCCAG    180
AAGGAAGCCA TCTCCCCTCC AGATGCGGCC TCAGCTGCTC CACTCCGAAC AATCACTGCT    240
GACACTTTCC GCAAACTCTT CCGAGTCTAC TCCAATTTCC TCCGGGGAAA GCTGAAGCTG    300
TACACAGGGG AGGCCTGCAG GACAGGGGAC AGATGAGGCG GCGGCTCCCC CCACCACGCC    360
TCATCTGTGA CAGCCGAGTC CTGGAGAGGT ACCTCTTGGA GGCCAAGGAG GCCGAGAATA    420
TCACGACGGG CTGTGCTGAA CACTGCAGCT TGAATGAGAA TAATCACTGT CCCAGACACC    480
AAAGTTAATT TCTATGCCTG GAAGAGGATG GAG                                 513
```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```
CAGGCCCTGT TGGTCAACTC TTCCCAGCCG TGGGAGCCCC TGCAGCTGCA TGTGGATAAA     60
GCCGTCAGTG GCCTTCGCAG CCTCACCACT CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA    120
GCCATCTCCC CTCCAGATGC GGCCTCAGCT GCTCCACTCC GAACAATCAC TGCTGACACT    180
TTCCGCAAAC TCTTCCGAGT CTACTCCAAT TTCCTCCGGG GAAAGCTGAA GCTGTACACA    240
GGGGAGGCCT GCAGGACAGG GGACAGATGA GGCGGCGGCT CCCCCCACCA CGCCTCATCT    300
GTGACAGCCG AGTCCTGGAG AGGTACCTCT TGGAGGCCAA GGAGGCCGAG AATATCACGA    360
CGGGCTGTGC TGAACACTGC AGCTTGAATG AGAATAATCA CTGTCCCAGA CACCAAAGTT    420
AATTTCTATG CCTGGAAGAG GATGGAGGTC GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC    480
CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG GGC                                 513
```

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```
GCCCTGTTGG TCAACTCTTC CCAGCCGTGG GAGCCCCTGC AGCTGCATGT GGATAAAGCC     60
GTCAGTGGCC TTCGCAGCCT CACCACTCTG CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC    120
ATCTCCCCTC CAGATGCGGC CTCAGCTGCT CCACTCCGAA CAATCACTGC TGACACTTTC    180
CGCAAACTCT TCCGAGTCTA CTCCAATTTC CTCCGGGGAA AGCTGAAGCT GTACACAGGG    240
GAGGCCTGCA GGACAGGGGA CAGATGAGGC GGCGGCTCCC CCCACCACGC CTCATCTGTG    300
ACAGCCGAGT CCTGGAGAGG TACCTCTTGG AGGCCAAGGA GGCCGAGAAT ATCACGACGG    360
GCTGTGCTGA ACACTGCAGC TTGAATGAGA ATAATCACTG TCCCAGACAC CAAAGTTAAT    420
TTCTATGCCT GGAAGAGGAT GGAGGTCGGG CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG    480
GCCCTGCTGT CGGAAGCTGT CCTGCGGGGC CAG                                 513
```

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```
CTGTTGGTCA ACTCTTCCCA GCCGTGGGAG CCCCTGCAGC TGCATGTGGA TAAAGCCGTC     60
AGTGGCCTTC GCAGCCTCAC CACTCTGCTT CGGGCTCTGG GAGCCCAGAA GGAAGCCATC    120
TCCCCTCCAG ATGCGGCCTC AGCTGCTCCA CTCCGAACAA TCACTGCTGA CACTTTCCGC    180
AAACTCTTCC GAGTCTACTC CAATTTCCTC CGGGGAAAGC TGAAGCTGTA CACAGGGGAG    240
GCCTGCAGGA CAGGGGACAG ATGAGGCGGC GGCTCCCCCC ACCACGCCTC ATCTGTGACA    300
GCCGAGTCCT GGAGAGGTAC CTCTTGGAGG CCAAGGAGGC CGAGAATATC ACGACGGGCT    360
GTGCTGAACA CTGCAGCTTG AATGAGAATA ATCACTGTCC CAGACACCAA AGTTAATTTC    420
TATGCCTGGA AGAGGATGGA GGTCGGGCAG CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC    480
CTGCTGTCGG AAGCTGTCCT GCGGGGCCAG GCC                                 513
```

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```
TTGGTCAACT CTTCCCAGCC GTGGGAGCCC CTGCAGCTGC ATGTGGATAA AGCCGTCAGT     60
GGCCTTCGCA GCCTCACCAC TCTGCTTCGG GCTCTGGGAG CCCAGAAGGA AGCCATCTCC    120
CCTCCAGATG CGGCCTCAGC TGCTCCACTC CGAACAATCA CTGCTGACAC TTTCCGCAAA    180
```

```
CTCTTCCGAG TCTACTCCAA TTTCCTCCGG GGAAAGCTGA AGCTGTACAC AGGGGAGGCC    240
TGCAGGACAG GGGACAGATG AGGCGGCGGC TCCCCCCACC ACGCCTCATC TGTGACAGCC    300
GAGTCCTGGA GAGGTACCTC TTGGAGGCCA AGGAGGCCGA GAATATCACG ACGGGCTGTG    360
CTGAACACTG CAGCTTGAAT GAGAATAATC ACTGTCCCAG ACACCAAAGT TAATTTCTAT    420
GCCTGGAAGA GGATGGAGGT CGGGCAGCAG GCCGTAGAAG TCTGGCAGGG CCTGGCCCTG    480
CTGTCGGAAG CTGTCCTGCG GGGCCAGGCC CTG                                 513
```

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
GTCAACTCTT CCCAGCCGTG GGAGCCCCTG CAGCTGCATG TGGATAAAGC CGTCAGTGGC     60
CTTCGCAGCC TCACCACTCT GCTTCGGGCT CTGGGAGCCC AGAAGGAAGC CATCTCCCCT    120
CCAGATGCGG CCTCAGCTGC TCCACTCCGA ACAATCACTG CTGACACTTT CCGCAAACTC    180
TTCCGAGTCT ACTCCAATTT CCTCCGGGGA AAGCTGAAGC TGTACACAGG GGAGGCCTGC    240
AGGACAGGGG ACAGATGAGG CGGCGGCTCC CCCCACCACG CCTCATCTGT GACAGCCGAG    300
TCCTGGAGAG GTACCTCTTG GAGGCCAAGG AGGCCGAGAA TATCACGACG GGCTGTGCTG    360
AACACTGCAG CTTGAATGAG AATAATCACT GTCCCAGACA CCAAAGTTAA TTTCTATGCC    420
TGGAAGAGGA TGGAGGTCGG GCAGCAGGCC GTAGAAGTCT GGCAGGGCCT GGCCCTGCTG    480
TCGGAAGCTG TCCTGCGGGG CCAGGCCCTG TTG                                 513
```

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
AACTCTTCCC AGCCGTGGGA GCCCCTGCAG CTGCATGTGG ATAAAGCCGT CAGTGGCCTT     60
CGCAGCCTCA CCACTCTGCT TCGGGCTCTG GGAGCCCAGA AGGAAGCCAT CTCCCCTCCA    120
GATGCGGCCT CAGCTGCTCC ACTCCGAACA ATCACTGCTG ACACTTTCCG CAAACTCTTC    180
CGAGTCTACT CCAATTTCCT CCGGGGAAAG CTGAAGCTGT ACACAGGGGA GGCCTGCAGG    240
ACAGGGGACA GATGAGGCGG CGGCTCCCCC CACCACGCCT CATCTGTGAC AGCCGAGTCC    300
TGGAGAGGTA CCTCTTGGAG GCCAAGGAGG CCGAGAATAT CACGACGGGC TGTGCTGAAC    360
ACTGCAGCTT GAATGAGAAT AATCACTGTC CCAGACACCA AAGTTAATTT CTATGCCTGG    420
AAGAGGATGG AGGTCGGGCA GCAGGCCGTA GAAGTCTGGC AGGGCCTGGC CCTGCTGTCG    480
GAAGCTGTCC TGCGGGGCCA GGCCCTGTTG GTC                                 513
```

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

```
TCTTCCCAGC CGTGGGAGCC CCTGCAGCTG CATGTGGATA AAGCCGTCAG TGGCCTTCGC     60
AGCCTCACCA CTCTGCTTCG GGCTCTGGGA GCCCAGAAGG AAGCCATCTC CCCTCCAGAT    120
GCGGCCTCAG CTGCTCCACT CCGAACAATC ACTGCTGACA CTTTCCGCAA ACTCTTCCGA    180
GTCTACTCCA ATTTCCTCCG GGGAAAGCTG AAGCTGTACA CAGGGGAGGC CTGCAGGACA    240
GGGGACAGAT GAGGCGGCGG CTCCCCCCAC CACGCCTCAT CTGTGACAGC CGAGTCCTGG    300
AGAGGTACCT CTTGGAGGCC AAGGAGGCCG AGAATATCAC GACGGGCTGT GCTGAACACT    360
GCAGCTTGAA TGAGAATAAT CACTGTCCCA GACACCAAAG TTAATTTCTA TGCCTGGAAG    420
AGGATGGAGG TCGGGCAGCA GGCCGTAGAA GTCTGGCAGG GCCTGGCCCT GCTGTCGGAA    480
GCTGTCCTGC GGGGCCAGGC CCTGTTGGTC AAC                                 513
```

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

```
TCCCAGCCGT GGGAGCCCCT GCAGCTGCAT GTGGATAAAG CCGTCAGTGG CCTTCGCAGC     60
CTCACCACTC TGCTTCGGGC TCTGGGAGCC CAGAAGGAAG CCATCTCCCC TCCAGATGCG    120
GCCTCAGCTG CTCCACTCCG AACAATCACT GCTGACACTT TCCGCAAACT CTTCCGAGTC    180
TACTCCAATT TCCTCCGGGG AAAGCTGAAG CTGTACACAG GGGAGGCCTG CAGGACAGGG    240
GACAGATGAG GCGGCGGCTC CCCCCACCAC GCCTCATCTG TGACAGCCGA GTCCTGGAGA    300
GGTACCTCTT GGAGGCCAAG GAGGCCGAGA ATATCACGAC GGGCTGTGCT GAACACTGCA    360
GCTTGAATGA GAATAATCAC TGTCCCAGAC ACCAAAGTTA ATTTCTATGC CTGGAAGAGG    420
ATGGAGGTCG GGCAGCAGGC CGTAGAAGTC TGGCAGGGCC TGGCCCTGCT GTCGGAAGCT    480
GTCCTGCGGG GCCAGGCCCT GTTGGTCAAC TCT                                  513
```

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

```
CAGCCGTGGG AGCCCCTGCA GCTGCATGTG GATAAAGCCG TCAGTGGCCT TCGCAGCCTC     60
ACCACTCTGC TTCGGGCTCT GGGAGCCCAG AAGGAAGCCA TCTCCCCTCC AGATGCGGCC    120
TCAGCTGCTC CACTCCGAAC AATCACTGCT GACACTTTCC GCAAACTCTT CCGAGTCTAC    180
TCCAATTTCC TCCGGGGAAA GCTGAAGCTG TACACAGGGG AGGCCTGCAG GACAGGGGAC    240
AGATGAGGCG GCGGCTCCCC CCACCACGCC TCATCTGTGA CAGCCGAGTC CTGGAGAGGT    300
ACCTCTTGGA GGCCAAGGAG GCCGAGAATA TCACGACGGG CTGTGCTGAA CACTGCAGCT    360
TGAATGAGAA TAATCACTGT CCCAGACACC AAAGTTAATT TCTATGCCTG GAAGAGGATG    420
GAGGTCGGGC AGCAGGCCGT AGAAGTCTGG CAGGGCCTGG CCCTGCTGTC GGAAGCTGTC    480
CTGCGGGGCC AGGCCCTGTT GGTCAACTCT TCC                                  513
```

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

```
CCGTGGGAGC CCCTGCAGCT GCATGTGGAT AAAGCCGTCA GTGGCCTTCG CAGCCTCACC     60
ACTCTGCTTC GGGCTCTGGG AGCCCAGAAG GAAGCCATCT CCCCTCCAGA TGCGGCCTCA    120
GCTGCTCCAC TCCGAACAAT CACTGCTGAC ACTTTCCGCA AACTCTTCCG AGTCTACTCC    180
AATTTCCTCC GGGGAAAGCT GAAGCTGTAC ACAGGGGAGG CCTGCAGGAC AGGGGACAGA    240
TGAGGCGGCG GCTCCCCCCA CCACGCCTCA TCTGTGACAG CCGAGTCCTG GAGAGGTACC    300
TCTTGGAGGC CAAGGAGGCC GAGAATATCA CGACGGGCTG TGCTGAACAC TGCAGCTTGA    360
ATGAGAATAA TCACTGTCCC AGACACCAAA GTTAATTTCT ATGCCTGGAA GAGGATGGAG    420
GTCGGGCAGC AGGCCGTAGA AGTCTGGCAG GGCCTGGCCC TGCTGTCGGA AGCTGTCCTG    480
CGGGGCCAGG CCCTGTTGGT CAACTCTTCC CAG                                  513
```

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

```
TGGGAGCCCC TGCAGCTGCA TGTGGATAAA GCCGTCAGTG GCCTTCGCAG CCTCACCACT     60
CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA GCCATCTCCC CTCCAGATGC GGCCTCAGCT    120
GCTCCACTCC GAACAATCAC TGCTGACACT TTCCGCAAAC TCTTCCGAGT CTACTCCAAT    180
TTCCTCCGGG GAAAGCTGAA GCTGTACACA GGGGAGGCCT GCAGGACAGG GGACAGATGA    240
GGCGGCGGCT CCCCCCACCA CGCCTCATCT GTGACAGCCG AGTCCTGGAG AGGTACCTCT    300
TGGAGGCCAA GGAGGCCGAG AATATCACGA CGGGCTGTGC TGAACACTGC AGCTTGAATG    360
AGAATAATCA CTGTCCCAGA CACCAAAGTT AATTTCTATG CCTGGAAGAG GATGGAGGTC    420
GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG    480
GGCCAGGCCC TGTTGGTCAA CTCTTCCCAG CCG                                  513
```

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

GAGCCCCTGC AGCTGCATGT GGATAAAGCC GTCAGTGGCC TTCGCAGCCT CACCACTCTG 60
CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC ATCTCCCCTC CAGATGCGGC CTCAGCTGCT 120
CCACTCCGAA CAATCACTGC TGACACTTTC CGCAAACTCT TCCGAGTCTA CTCCAATTTC 180
CTCCGGGGAA AGCTGAAGCT GTACACAGGG GAGGCCTGCA GGACAGGGGA CAGATGAGGC 240
GGCGGCTCCC CCCACCACGC CTCATCTGTG ACAGCCGAGT CCTGGAGAGG TACCTCTTGG 300
AGGCCAAGGA GGCCGAGAAT ATCACGACGG GCTGTGCTGA ACACTGCAGC TTGAATGAGA 360
ATAATCACTG TCCCAGACAC CAAAGTTAAT TTCTATGCCT GGAAGAGGAT GGAGGTCGGG 420
CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG GCCCTGCTGT CGGAAGCTGT CCTGCGGGGC 480
CAGGCCCTGT TGGTCAACTC TTCCCAGCCG TGG 513

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC ATCTCCCCTC CAGATGCGGC CTCAGCTGCT 60
CCACTCCGAA CAATCACTGC TGACACTTTC CGCAAACTCT TCCGAGTCTA CTCCAATTTC 120
CTCCGGGGAA AGCTGAAGCT GTACACAGGG GAGGCCTGCA GGACAGGGGA CAGATGAGGC 180
GGCGGCTCCC CCCACCACGC CTCATCTGTG ACAGCCGAGT CCTGGAGAGG TACCTCTTGG 240
AGGCCAAGGA GGCCGAGAAT ATCACGACGG GCTGTGCTGA ACACTGCAGC TTGAATGAGA 300
ATAATCACTG TCCCAGACAC CAAAGTTAAT TTCTATGCCT GGAAGAGGAT GGAGGTCGGG 360
CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG GCCCTGCTGT CGGAAGCTGT CCTGCGGGGC 420
CAGGCCCTGT TGGTCAACTC TTCCCAGCCG TGGGAGCCCC TGCAGCTGCA TGTGGATAAA 480
GCCGTCAGTG GCCTTCGCAG CCTCACCACT CTG 513

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

CGGGCTCTGG GAGCCCAGAA GGAAGCCATC TCCCCTCCAG ATGCGGCCTC AGCTGCTCCA 60
CTCCGAACAA TCACTGCTGA CACTTTCCGC AAACTCTTCC GAGTCTACTC CAATTTCCTC 120
CGGGGAAAGC TGAAGCTGTA CACAGGGGAG GCCTGCAGGA CAGGGGACAG ATGAGGCGGC 180
GGCTCCCCCC ACCACGCCTC ATCTGTGACA GCCGAGTCCT GGAGAGGTAC CTCTTGGAGG 240
CCAAGGAGGC CGAGAATATC ACGACGGGCT GTGCTGAACA CTGCAGCTTG AATGAGAATA 300
ATCACTGTCC CAGACACCAA AGTTAATTTC TATGCCTGGA AGAGGATGGA GGTCGGGCAG 360
CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC CTGCTGTCGG AAGCTGTCCT GCGGGGCCAG 420
GCCCTGTTGG TCAACTCTTC CCAGCCGTGG GAGCCCCTGC AGCTGCATGT GGATAAAGCC 480
GTCAGTGGCC TTCGCAGCCT CACCACTCTG CTT 513

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GCTCTGGGAG CCCAGAAGGA AGCCATCTCC CCTCCAGATG CGGCCTCAGC TGCTCCACTC 60
CGAACAATCA CTGCTGACAC TTTCCGCAAA CTCTTCCGAG TCTACTCCAA TTTCCTCCGG 120
GGAAAGCTGA AGCTGTACAC AGGGGAGGCC TGCAGGACAG GGGACAGATG AGGCGGCGGC 180

```
TCCCCCCACC ACGCCTCATC TGTGACAGCC GAGTCCTGGA GAGGTACCTC TTGGAGGCCA    240
AGGAGGCCGA GAATATCACG ACGGGCTGTG CTGAACACTG CAGCTTGAAT GAGAATAATC    300
ACTGTCCCAG ACACCAAAGT TAATTTCTAT GCCTGGAAGA GGATGGAGGT CGGGCAGCAG    360
GCCGTAGAAG TCTGGCAGGG CCTGGCCCTG CTGTCGGAAG CTGTCCTGCG GGGCCAGGCC    420
CTGTTGGTCA ACTCTTCCCA GCCGTGGGAG CCCCTGCAGC TGCATGTGGA TAAAGCCGTC    480
AGTGGCCTTC GCAGCCTCAC CACTCTGCTT CGG                                 513
```

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

```
CTGGGAGCCC AGAAGGAAGC CATCTCCCCT CCAGATGCGG CCTCAGCTGC TCCACTCCGA     60
ACAATCACTG CTGACACTTT CCGCAAACTC TTCCGAGTCT ACTCCAATTT CCTCCGGGGA    120
AAGCTGAAGC TGTACACAGG GGAGGCCTGC AGGACAGGGG ACAGATGAGG CGGCGGCTCC    180
CCCCACCACG CCTCATCTGT GACAGCCGAG TCCTGGAGAG GTACCTCTTG GAGGCCAAGG    240
AGGCCGAGAA TATCACGACG GGCTGTGCTG AACACTGCAG CTTGAATGAG AATAATCACT    300
GTCCCAGACA CCAAAGTTAA TTTCTATGCC TGGAAGAGGA TGGAGGTCGG GCAGCAGGCC    360
GTAGAAGTCT GGCAGGGCCT GGCCCTGCTG TCGGAAGCTG TCCTGCGGGG CCAGGCCCTG    420
TTGGTCAACT CTTCCCAGCC GTGGGAGCCC CTGCAGCTGC ATGTGGATAA AGCCGTCAGT    480
GGCCTTCGCA GCCTCACCAC TCTGCTTCGG GTC                                 513
```

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

```
GGAGCCCAGA AGGAAGCCAT CTCCCCTCCA GATGCGGCCT CAGCTGCTCC ACTCCGAACA     60
ATCACTGCTG ACACTTTCCG CAAACTCTTC CGAGTCTACT CCAATTTCCT CCGGGGAAAG    120
CTGAAGCTGT ACACAGGGGA GGCCTGCAGG ACAGGGGACA GATGAGGCGG CGGCTCCCCC    180
CACCACGCCT CATCTGTGAC AGCCGAGTCC TGGAGAGGTA CCTCTTGGAG GCCAAGGAGG    240
CCGAGAATAT CACGACGGGC TGTGCTGAAC ACTGCAGCTT GAATGAGAAT AATCACTGTC    300
CCAGACACCA AAGTTAATTT CTATGCCTGG AAGAGGATGG AGGTCGGGCA GCAGGCCGTA    360
GAAGTCTGGC AGGGCCTGGC CCTGCTGTCG GAAGCTGTCC TGCGGGGCCA GGCCCTGTTG    420
GTCAACTCTT CCCAGCCGTG GGAGCCCCTG CAGCTGCATG TGGATAAAGC CGTCAGTGGC    480
CTTCGCAGCC TCACCACTCT GCTTCGGGCT CTG                                 513
```

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

```
GCCCAGAAGG AAGCCATCTC CCCTCCAGAT GCGGCCTCAG CTGCTCCACT CCGAACAATC     60
ACTGCTGACA CTTTCCGCAA ACTCTTCCGA GTCTACTCCA ATTTCCTCCG GGGAAAGCTG    120
AAGCTGTACA CAGGGGAGGC CTGCAGGACA GGGGACAGAT GAGGCGGCGG CTCCCCCCAC    180
CACGCCTCAT CTGTGACAGC CGAGTCCTGG AGAGGTACCT CTTGGAGGCC AAGGAGGCCG    240
AGAATATCAC GACGGGCTGT GCTGAACACT GCAGCTTGAA TGAGAATAAT CACTGTCCCA    300
GACACCAAAG TTAATTTCTA TGCCTGGAAG AGGATGGAGG TCGGGCAGCA GGCCGTAGAA    360
GTCTGGCAGG GCCTGGCCCT GCTGTCGGAA GCTGTCCTGC GGGGCCAGGC CCTGTTGGTC    420
AACTCTTCCC AGCCGTGGGA GCCCCTGCAG CTGCATGTGG ATAAAGCCGT CAGTGGCCTT    480
CGCAGCCTCA CCACTCTGCT TCGGGCTCTG GGA                                 513
```

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

```
CAGAAGGAAG CCATCTCCCC TCCAGATGCG GCCTCAGCTG CTCCACTCCG AACAATCACT     60
GCTGACACTT TCCGCAAACT CTTCCGAGTC TACTCCAATT TCCTCCGGGG AAAGCTGAAG    120
CTGTACACAG GGGAGGCCTG CAGGACAGGG GACAGATGAG GCGGCGGCTC CCCCCACCAC    180
GCCTCATCTG TGACAGCCGA GTCCTGGAGA GGTACCTCTT GGAGGCCAAG GAGGCCGAGA    240
ATATCACGAC GGGCTGTGCT GAACACTGCA GCTTGAATGA GAATAATCAC TGTCCCAGAC    300
ACCAAAGTTA ATTTCTATGC CTGGAAGAGG ATGGAGGTCG GGCAGCAGGC CGTAGAAGTC    360
TGGCAGGGCC TGGCCCTGCT GTCGGAAGCT GTCCTGCGGG GCCAGGCCCT GTTGGTCAAC    420
TCTTCCCAGC CGTGGGAGCC CCTGCAGCTG CATGTGGATA AAGCCGTCAG TGGCCTTCGC    480
AGCCTCACCA CTCTGCTTCG GGCTCTGGGA GCC                                 513
```

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

```
AAGGAAGCCA TCTCCCCTCC AGATGCGGCC TCAGCTGCTC CACTCCGAAC AATCACTGCT     60
GACACTTTCC GCAAACTCTT CCGAGTCTAC TCCAATTTCC TCCGGGGAAA GCTGAAGCTG    120
TACACAGGGG AGGCCTGCAG GACAGGGGAC AGATGAGGCG GCGGCTCCCC CCACCACGCC    180
TCATCTGTGA CAGCCGAGTC CTGGAGAGGT ACCTCTTGGA GGCCAAGGAG GCCGAGAATA    240
TCACGACGGG CTGTGCTGAA CACTGCAGCT TGAATGAGAA TAATCACTGT CCCAGACACC    300
AAAGTTAATT TCTATGCCTG GAAGAGGATG GAGGTCGGGC AGCAGGCCGT AGAAGTCTGG    360
CAGGGCCTGG CCCTGCTGTC GGAAGCTGTC CTGCGGGGCC AGGCCCTGTT GGTCAACTCT    420
TCCCAGCCGT GGGAGCCCCT GCAGCTGCAT GTGGATAAAG CCGTCAGTGG CCTTCGCAGC    480
CTCACCACTC TGCTTCGGGC TCTGGGAGCC CAG                                 513
```

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

```
GAAGCCATCT CCCCTCCAGA TGCGGCCTCA GCTGCTCCAC TCCGAACAAT CACTGCTGAC     60
ACTTTCCGCA AACTCTTCCG AGTCTACTCC AATTTCCTCC GGGGAAAGCT GAAGCTGTAC    120
ACAGGGGAGG CCTGCAGGAC AGGGGACAGA TGAGGCGGCG GCTCCCCCCA CCACGCCTCA    180
TCTGTGACAG CCGAGTCCTG GAGAGGTACC TCTTGGAGGC CAAGGAGGCC GAGAATATCA    240
CGACGGGCTG TGCTGAACAC TGCAGCTTGA ATGAGAATAA TCACTGTCCC AGACACCAAA    300
GTTAATTTCT ATGCCTGGAA GAGGATGGAG GTCGGGCAGC AGGCCGTAGA AGTCTGGCAG    360
GGCCTGGCCC TGCTGTCGGA AGCTGTCCTG CGGGGCCAGG CCCTGTTGGT CAACTCTTCC    420
CAGCCGTGGG AGCCCCTGCA GCTGCATGTG GATAAAGCCG TCAGTGGCCT TCGCAGCCTC    480
ACCACTCTGC TTCGGGCTCT GGGAGCCCAG AAG                                 513
```

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

```
GCCATCTCCC CTCCAGATGC GGCCTCAGCT GCTCCACTCC GAACAATCAC TGCTGACACT     60
TTCCGCAAAC TCTTCCGAGT CTACTCCAAT TTCCTCCGGG GAAAGCTGAA GCTGTACACA    120
GGGGAGGCCT GCAGGACAGG GGACAGATGA GGCGGCGGCT CCCCCCACCA CGCCTCATCT    180
GTGACAGCCG AGTCCTGGAG AGGTACCTCT TGGAGGCCAA GGAGGCCGAG AATATCACGA    240
CGGGCTGTGC TGAACACTGC AGCTTGAATG AGAATAATCA CTGTCCCAGA CACCAAAGTT    300
AATTTCTATG CCTGGAAGAG GATGGAGGTC GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC    360
CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG GGCCAGGCCC TGTTGGTCAA CTCTTCCCAG    420
CCGTGGGAGC CCCTGCAGCT GCATGTGGAT AAAGCCGTCA GTGGCCTTCG CAGCCTCACC    480
ACTCTGCTTC GGGCTCTGGG AGCCCAGAAG GAA                                 513
```

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

ATCTCCCCTC CAGATGCGGC CTCAGCTGCT CCACTCCGAA CAATCACTGC TGACACTTTC 60
CGCAAACTCT TCCGAGTCTA CTCCAATTTC CTCCGGGGAA AGCTGAAGCT GTACACAGGG 120
GAGGCCTGCA GGACAGGGGA CAGATGAGGC GGCGGCTCCC CCCACCACGC CTCATCTGTG 180
ACAGCCGAGT CCTGGAGAGG TACCTCTTGG AGGCCAAGGA GGCCGAGAAT ATCACGACGG 240
GCTGTGCTGA ACACTGCAGC TTGAATGAGA ATAATCACTG TCCCAGACAC CAAAGTTAAT 300
TTCTATGCCT GGAAGAGGAT GGAGGTCGGG CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG 360
GCCCTGCTGT CGGAAGCTGT CCTGCGGGGC CAGGCCCTGT TGGTCAACTC TTCCCAGCCG 420
TGGGAGCCCC TGCAGCTGCA TGTGGATAAA GCCGTCAGTG GCCTTCGCAG CCTCACCACT 480
CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA GCC 513

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

TCCCCTCCAG ATGCGGCCTC AGCTGCTCCA CTCCGAACAA TCACTGCTGA CACTTTCCGC 60
AAACTCTTCC GAGTCTACTC CAATTTCCTC CGGGGAAAGC TGAAGCTGTA CACAGGGGAG 120
GCCTGCAGGA CAGGGGACAG ATGAGGCGGC GGCTCCCCCC ACCACGCCTC ATCTGTGACA 180
GCCGAGTCCT GGAGAGGTAC CTCTTGGAGG CCAAGGAGGC CGAGAATATC ACGACGGGCT 240
GTGCTGAACA CTGCAGCTTG AATGAGAATA ATCACTGTCC CAGACACCAA AGTTAATTTC 300
TATGCCTGGA AGAGGATGGA GGTCGGGCAG CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC 360
CTGCTGTCGG AAGCTGTCCT GCGGGGCCAG GCCCTGTTGG TCAACTCTTC CCAGCCGTGG 420
GAGCCCCTGC AGCTGCATGT GGATAAAGCC GTCAGTGGCC TTCGCAGCCT CACCACTCTG 480
CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC ATC 513

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

CCTCCAGATG CGGCCTCAGC TGCTCCACTC CGAACAATCA CTGCTGACAC TTTCCGCAAA 60
CTCTTCCGAG TCTACTCCAA TTTCCTCCGG GGAAAGCTGA AGCTGTACAC AGGGGAGGCC 120
TGCAGGACAG GGGACAGATG AGGCGGCGGC TCCCCCCACC ACGCCTCATC TGTGACAGCC 180
GAGTCCTGGA GAGGTACCTC TTGGAGGCCA AGGAGGCCGA GAATATCACG ACGGGCTGTG 240
CTGAACACTG CAGCTTGAAT GAGAATAATC ACTGTCCCAG ACACCAAAGT TAATTTCTAT 300
GCCTGGAAGA GGATGGAGGT CGGGCAGCAG GCCGTAGAAG TCTGGCAGGG CCTGGCCCTG 360
CTGTCGGAAG CTGTCCTGCG GGGCCAGGCC CTGTTGGTCA ACTCTTCCCA GCCGTGGGAG 420
CCCCTGCAGC TGCATGTGGA TAAAGCCGTC AGTGGCCTTC GCAGCCTCAC CACTCTGCTT 480
CGGGCTCTGG GAGCCCAGAA GGAAGCCATC TCC 513

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

CCAGATGCGG CCTCAGCTGC TCCACTCCGA ACAATCACTG CTGACACTTT CCGCAAACTC 60
TTCCGAGTCT ACTCCAATTT CCTCCGGGGA AAGCTGAAGC TGTACACAGG GGAGGCCTGC 120
AGGACAGGGG ACAGATGAGG CGGCGGCTCC CCCCACCACG CCTCATCTGT GACAGCCGAG 180

TCCTGGAGAG GTACCTCTTG GAGGCCAAGG AGGCCGAGAA TATCACGACG GGCTGTGCTG 240
AACACTGCAG CTTGAATGAG AATAATCACT GTCCCAGACA CCAAAGTTAA TTTCTATGCC 300
TGGAAGAGGA TGGAGGTCGG GCAGCAGGCC GTAGAAGTCT GGCAGGGCCT GGCCCTGCTG 360
TCGGAAGCTG TCCTGCGGGG CCAGGCCCTG TTGGTCAACT CTTCCCAGCC GTGGGAGCCC 420
CTGCAGCTGC ATGTGGATAA AGCCGTCAGT GGCCTTCGCA GCCTCACCAC TCTGCTTCGG 480
GCTCTGGGAG CCCAGAAGGA AGCCATCTCC CCT 513

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

GATGCGGCCT CAGCTGCTCC ACTCCGAACA ATCACTGCTG ACACTTTCCG CAAACTCTTC 60
CGAGTCTACT CCAATTTCCT CCGGGGAAAG CTGAAGCTGT ACACAGGGGA GGCCTGCAGG 120
ACAGGGGACA GATGAGGCGG CGGCTCCCCC CACCACGCCT CATCTGTGAC AGCCGAGTCC 180
TGGAGAGGTA CCTCTTGGAG GCCAAGGAGG CCGAGAATAT CACGACGGGC TGTGCTGAAC 240
ACTGCAGCTT GAATGAGAAT AATCACTGTC CCAGACACCA AAGTTAATTT CTATGCCTGG 300
AAGAGGATGG AGGTCGGGCA GCAGGCCGTA GAAGTCTGGC AGGGCCTGGC CCTGCTGTCG 360
GAAGCTGTCC TGCGGGGCCA GGCCCTGTTG GTCAACTCTT CCCAGCCGTG GGAGCCCCTG 420
CAGCTGCATG TGGATAAAGC CGTCAGTGGC CTTCGCAGCC TCACCACTCT GCTTCGGGCT 480
CTGGGAGCCC AGAAGGAAGC CATCTCCCCT CCA 513

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

GCGGCCTCAG CTGCTCCACT CCGAACAATC ACTGCTGACA CTTTCCGCAA ACTCTTCCGA 60
GTCTACTCCA ATTTCCTCCG GGGAAAGCTG AAGCTGTACA CAGGGGAGGC CTGCAGGACA 120
GGGGACAGAT GAGGCGGCGG CTCCCCCCAC CACGCCTCAT CTGTGACAGC CGAGTCCTGG 180
AGAGGTACCT CTTGGAGGCC AAGGAGGCCG AGAATATCAC GACGGGCTGT GCTGAACACT 240
GCAGCTTGAA TGAGAATAAT CACTGTCCCA GACACCAAAG TTAATTTCTA TGCCTGGAAG 300
AGGATGGAGG TCGGGCAGCA GGCCGTAGAA GTCTGGCAGG GCCTGGCCCT GCTGTCGGAA 360
GCTGTCCTGC GGGGCCAGGC CCTGTTGGTC AACTCTTCCC AGCCGTGGGA GCCCCTGCAG 420
CTGCATGTGG ATAAAGCCGT CAGTGGCCTT CGCAGCCTCA CCACTCTGCT TCGGGCTCTG 480
GGAGCCCAGA AGGAAGCCAT CTCCCCTCCA GAT 513

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

GCCTCAGCTG CTCCACTCCG AACAATCACT GCTGACACTT TCCGCAAACT CTTCCGAGTC 60
TACTCCAATT TCCTCCGGGG AAAGCTGAAG CTGTACACAG GGGAGGCCTG CAGGACAGGG 120
GACAGATGAG GCGGCGGCTC CCCCCACCAC GCCTCATCTG TGACAGCCGA GTCCTGGAGA 180
GGTACCTCTT GGAGGCCAAG GAGGCCGAGA ATATCACGAC GGGCTGTGCT GAACACTGCA 240
GCTTGAATGA GAATAATCAC TGTCCCAGAC ACCAAAGTTA ATTTCTATGC CTGGAAGAGG 300
ATGGAGGTCG GGCAGCAGGC CGTAGAAGTC TGGCAGGGCC TGGCCCTGCT GTCGGAAGCT 360
GTCCTGCGGG GCCAGGCCCT GTTGGTCAAC TCTTCCCAGC CGTGGGAGCC CCTGCAGCTG 420
CATGTGGATA AAGCCGTCAG TGGCCTTCGC AGCCTCACCA CTCTGCTTCG GGCTCTGGGA 480
GCCCAGAAGG AAGCCATCTC CCCTCCAGAT GCG 513

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

```
TCAGCTGCTC CACTCCGAAC AATCACTGCT GACACTTTCC GCAAACTCTT CCGAGTCTAC     60
TCCAATTTCC TCCGGGGAAA GCTGAAGCTG TACACAGGGG AGGCCTGCAG GACAGGGGAC    120
AGATGAGGCG GCGGCTCCCC CCACCACGCC TCATCTGTGA CAGCCGAGTC CTGGAGAGGT    180
ACCTCTTGGA GGCCAAGGAG GCCGAGAATA TCACGACGGG CTGTGCTGAA CACTGCAGCT    240
TGAATGAGAA TAATCACTGT CCCAGACACC AAAGTTAATT TCTATGCCTG GAAGAGGATG    300
GAGGTCGGGC AGCAGGCCGT AGAAGTCTGG CAGGGCCTGG CCCTGCTGTC GGAAGCTGTC    360
CTGCGGGGCC AGGCCCTGTT GGTCAACTCT TCCCAGCCGT GGGAGCCCCT GCAGCTGCAT    420
GTGGATAAAG CCGTCAGTGG CCTTCGCAGC CTCACCACTC TGCTTCGGGC TCTGGGAGCC    480
CAGAAGGAAG CCATCTCCCC TCCAGATGCG GCC                                 513
```

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

```
GCTGCTCCAC TCCGAACAAT CACTGCTGAC ACTTTCCGCA AACTCTTCCG AGTCTACTCC     60
AATTTCCTCC GGGGAAAGCT GAAGCTGTAC ACAGGGGAGG CCTGCAGGAC AGGGGACAGA    120
TGAGGCGGCG GCTCCCCCCA CCACGCCTCA TCTGTGACAG CCGAGTCCTG GAGAGGTACC    180
TCTTGGAGGC CAAGGAGGCC GAGAATATCA CGACGGGCTG TGCTGAACAC TGCAGCTTGA    240
ATGAGAATAA TCACTGTCCC AGACACCAAA GTTAATTTCT ATGCCTGGAA GAGGATGGAG    300
GTCGGGCAGC AGGCCGTAGA AGTCTGGCAG GGCCTGGCCC TGCTGTCGGA AGCTGTCCTG    360
CGGGGCCAGG CCCTGTTGGT CAACTCTTCC CAGCCGTGGG AGCCCCTGCA GCTGCATGTG    420
GATAAAGCCG TCAGTGGCCT TCGCAGCCTC ACCACTCTGC TTCGGGCTCT GGGAGCCCAG    480
AAGGAAGCCA TCTCCCCTCC AGATGCGGCC TCA                                 513
```

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

```
GCTCCACTCC GAACAATCAC TGCTGACACT TTCCGCAAAC TCTTCCGAGT CTACTCCAAT     60
TTCCTCCGGG GAAAGCTGAA GCTGTACACA GGGGAGGCCT GCAGGACAGG GGACAGATGA    120
GGCGGCGGCT CCCCCCACCA CGCCTCATCT GTGACAGCCG AGTCCTGGAG AGGTACCTCT    180
TGGAGGCCAA GGAGGCCGAG AATATCACGA CGGGCTGTGC TGAACACTGC AGCTTGAATG    240
AGAATAATCA CTGTCCCAGA CACCAAAGTT AATTTCTATG CCTGGAAGAG GATGGAGGTC    300
GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG    360
GGCCAGGCCC TGTTGGTCAA CTCTTCCCAG CCGTGGGAGC CCCTGCAGCT GCATGTGGAT    420
AAAGCCGTCA GTGGCCTTCG CAGCCTCACC ACTCTGCTTC GGGCTCTGGG AGCCCAGAAG    480
GAAGCCATCT CCCCTCCAGA TGCGGCCTCA GCT                                 513
```

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

```
CCACTCCGAA CAATCACTGC TGACACTTTC CGCAAACTCT TCCGAGTCTA CTCCAATTTC     60
CTCCGGGGAA AGCTGAAGCT GTACACAGGG GAGGCCTGCA GGACAGGGGA CAGATGAGGC    120
GGCGGCTCCC CCCACCACGC CTCATCTGTG ACAGCCGAGT CCTGGAGAGG TACCTCTTGG    180
AGGCCAAGGA GGCCGAGAAT ATCACGACGG GCTGTGCTGA ACACTGCAGC TTGAATGAGA    240
ATAATCACTG TCCCAGACAC CAAAGTTAAT TTCTATGCCT GGAAGAGGAT GGAGGTCGGG    300
CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG GCCCTGCTGT CGGAAGCTGT CCTGCGGGGC    360
CAGGCCCTGT TGGTCAACTC TTCCCAGCCG TGGGAGCCCC TGCAGCTGCA TGTGGATAAA    420
GCCGTCAGTG GCCTTCGCAG CCTCACCACT CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA    480
GCCATCTCCC CTCCAGATGC GGCCTCAGCT GCT                                 513
```

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

CTCCGAACAA TCACTGCTGA CACTTTCCGC AAACTCTTCC GAGTCTACTC CAATTTCCTC 60
CGGGGAAAGC TGAAGCTGTA CACAGGGGAG GCCTGCAGGA CAGGGGACAG ATGAGGCGGC 120
GGCTCCCCCC ACCACGCCTC ATCTGTGACA GCCGAGTCCT GGAGAGGTAC CTCTTGGAGG 180
CCAAGGAGGC CGAGAATATC ACGACGGGCT GTGCTGAACA CTGCAGCTTG AATGAGAATA 240
ATCACTGTCC CAGACACCAA AGTTAATTTC TATGCCTGGA AGAGGATGGA GGTCGGGCAG 300
CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC CTGCTGTCGG AAGCTGTCCT GCGGGGCCAG 360
GCCCTGTTGG TCAACTCTTC CCAGCCGTGG GAGCCCCTGC AGCTGCATGT GGATAAAGCC 420
GTCAGTGGCC TTCGCAGCCT CACCACTCTG CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC 480
ATCTCCCCTC CAGATGCGGC CTCAGCTGCT CCA 513

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

CGAACAATCA CTGCTGACAC TTTCCGCAAA CTCTTCCGAG TCTACTCCAA TTTCCTCCGG 60
GGAAAGCTGA AGCTGTACAC AGGGGAGGCC TGCAGGACAG GGGACAGATG AGGCGGCGGC 120
TCCCCCCACC ACGCCTCATC TGTGACAGCC GAGTCCTGGA GAGGTACCTC TTGGAGGCCA 180
AGGAGGCCGA GAATATCACG ACGGGCTGTG CTGAACACTG CAGCTTGAAT GAGAATAATC 240
ACTGTCCCAG ACACCAAAGT TAATTTCTAT GCCTGGAAGA GGATGGAGGT CGGGCAGCAG 300
GCCGTAGAAG TCTGGCAGGG CCTGGCCCTG CTGTCGGAAG CTGTCCTGCG GGGCCAGGCC 360
CTGTTGGTCA ACTCTTCCCA GCCGTGGGAG CCCCTGCAGC TGCATGTGGA TAAAGCCGTC 420
AGTGGCCTTC GCAGCCTCAC CACTCTGCTT CGGGCTCTGG GAGCCCAGAA GGAAGCCATC 480
TCCCCTCCAG ATGCGGCCTC AGCTGCTCCA CTC 513

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

ACAATCACTG CTGACACTTT CCGCAAACTC TTCCGAGTCT ACTCCAATTT CCTCCGGGGA 60
AAGCTGAAGC TGTACACAGG GGAGGCCTGC AGGACAGGGG ACAGATGAGG CGGCGGCTCC 120
CCCCACCACG CCTCATCTGT GACAGCCGAG TCCTGGAGAG GTACCTCTTG GAGGCCAAGG 180
AGGCCGAGAA TATCACGACG GGCTGTGCTG AACACTGCAG CTTGAATGAG AATAATCACT 240
GTCCCAGACA CCAAAGTTAA TTTCTATGCC TGGAAGAGGA TGGAGGTCGG GCAGCAGGCC 300
GTAGAAGTCT GGCAGGGCCT GGCCCTGCTG TCGGAAGCTG TCCTGCGGGG CCAGGCCCTG 360
TTGGTCAACT CTTCCCAGCC GTGGGAGCCC CTGCAGCTGC ATGTGGATAA AGCCGTCAGT 420
GGCCTTCGCA GCCTCACCAC TCTGCTTCGG GCTCTGGGAG CCCAGAAGGA AGCCATCTCC 480
CCTCCAGATG CGGCCTCAGC TGCTCCACTC CGA 513

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 501 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

GCCCCACCAC GCCTCATCTG TGACAGCCGA GTCCTGGAGA GGTACCTCTT GGAGGCCAAG 60
GAGGCCGAGA ATATCACGAC GGGCTGTGCT GAACACTGCA GCTTGAATGA GAATATCACT 120
GTCCCAGACA CCAAAGTTAA TTTCTATGCC TGGAAGAGGA TGGAGGTCGG GCAGCAGGCC 180

GTAGAAGTCT GGCAGGGCCT GGCCCTGCTG TCGGAAGCTG TCCTGCGGGG CCAGGCCCTG 240
TTGGTCAACT CTTCCCAGCC GTGGGAGCCC CTGCAGCTGC ATGTGGATAA AGCCGTCAGT 300
GGCCTTCGCA GCCTCACCAC TCTGCTTCGG GCTCTGGGAG CCCAGAAGGA AGCCATCTCC 360
CCTCCAGATG CGGCCTCAGC TGCTCCACTC CGAACAATCA CTGCTGACAC TTTCCGCAAA 420
CTCTTCCGAG TCTACTCCAA TTTCCTCCGG GGAAAGCTGA AGCTGTACAC AGGGGAGGCC 480
TGCAGGACAG GGGACAGATG A 501

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 166 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
1 5 10 15
Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
20 25 30
Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe
35 40 45
Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
50 55 60
Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
65 70 75 80
Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
85 90 95
Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
100 105 110
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
115 120 125
Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
130 135 140
Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
145 150 155 160
Cys Arg Thr Gly Asp Arg
165

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
1 5 10 15
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
20 25 30
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
35 40 45
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
50 55 60
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
65 70 75 80
Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala
85 90 95
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly
100 105 110
Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly
115 120 125
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu
130 135 140
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
145 150 155 160
Ala Glu His Cys Ser Leu Asn Glu Asn Ile
165 170

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Gly Gly Gly Ser
1

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Gly Gly Gly Ser Gly Gly Gly Ser
1 5

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Ser Gly Gly Ser Gly Gly Ser
1 5

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Glu Phe Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Glu Phe Gly Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Glu Phe Gly Gly Asn Gly Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Gly Gly Ser Asp Met Ala Gly
1 5

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

GCGCGCCCAT GGACAATCAC TGCTGAC 27

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

TCTGTCCCCT GTCCT 15

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

GCGCGCAAGC TTATTATCGG AGTGGAGCAG CTGAGGCCGC ATC 43

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

GCCCCACCAC GCCTCATCTG T 21

WHAT IS CLAIMED IS:

1. A human EPO receptor agonist polypeptide, comprising a modified EPO amino acid sequence of the Formula:

AlaProProArgLeuIleCysAspSerArgValLeuGluArgTyrLeuLeuGluAlaLys
10 20

GluAlaGluAsnIleThrThrGlyCysAlaGluHisCysSerLeuAsnGluAsnIleThr
30 40

ValProAspThrLysValAsnPheTyrAlaTrpLysArgMetGluValGlyGlnGlnAla
50 60

ValGluValTrpGlnGlyLeuAlaLeuLeuSerGluAlaValLeuArgGlyGlnAlaLeu
70 80

LeuValAsnSerSerGlnProTrpGluProLeuGlnLeuHisValAspLysAlaValSer
90 100

GlyLeuArgSerLeuThrThrLeuLeuArgAlaLeuGlyAlaGlnLysGluAlaIleSer
110 120

ProProAspAlaAlaSerAlaAlaProLeuArgThrIleThrAlaAspThrPheArgLys
130 140

LeuPheArgValTyrSerAsnPheLeuArgGlyLysLeuLysLeuTyrThrGlyGluAla
150 160

CysArgThrGlyAspArg SEQ ID NO:121
166

wherein optionally 1-6 amino acids from the N-terminus and 1-5 from the C-terminus can be deleted from said EPO receptor agonist polypeptide;

wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-termini at amino acids;

23-24	48-49	111-112
24-25	50-51	112-113
25-26	51-52	113-114
26-27	52-53	114-115
27-28	53-54	115-116
28-29	54-55	116-117
29-30	55-56	117-118
30-31	56-57	118-119

31-32	57-58	119-120
32-33	77-78	120-121
33-34	78-79	121-122
34-35	79-80	122-123
35-36	80-81	123-124
36-37	81-82	124-125
37-38	82-83	125-126
38-39	84-85	126-127
40-41	85-86	127-128
41-42	86-87	128-129
43-44	87-88	129-130
44-45	88-89	130-131
45-46	108-109	131-132
46-47	109-110	respectively; and
47-48	110-111	

said EPO receptor agonist polypeptide may optionally be immediately preceded by (methionine^{-1}), (alanine^{-1}) or (methionine^{-2}, alanine^{-1}).

2. The EPO receptor agonist polypeptide, as recited in claim 1, wherein said linker is selected from the group consisting of;

GlyGlyGlySer SEQ ID NO:123;

GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;

GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:125;

SerGlyGlySerGlyGlySer SEQ ID NO:126;

GluPheGlyAsnMet SEQ ID NO:127;

GluPheGlyGlyAsnMet SEQ ID NO:128;

GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and

GlyGlySerAspMetAlaGly SEQ ID NO:130.

3. The EPO receptor agonist polypeptide of claim 1 selected from the group consisting of;

SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17; SEQ ID NO:18; SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; SEQ ID NO:23; SEQ ID NO:24; SEQ ID NO:25; SEQ ID

NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:29; SEQ ID NO:30; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; SEQ ID NO:40; SEQ ID NO:41; SEQ ID NO:42; SEQ ID NO:43; SEQ ID NO:44; SEQ ID NO:45; SEQ ID NO:46; SEQ ID NO:47; SEQ ID NO:48; SEQ ID NO:49; SEQ ID NO:50; SEQ ID NO:51; SEQ ID NO:52; SEQ ID NO:53; SEQ ID NO:54; SEQ ID NO:55; SEQ ID NO:56; SEQ ID NO:57; SEQ ID NO:58; SEQ ID NO:59 and SEQ ID NO:122.

4. The EPO receptor agonist polypeptide of claim 3 wherein the linker sequence (GlyGlyGlyGlySer SEQ ID NO:123) is replaced by a linker sequence selected from the group consisting of;

GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;
GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:125;
SerGlyGlySerGlyGlySer SEQ ID NO:126;
GluPheGlyAsnMet SEQ ID NO:127;
GluPheGlyGlyAsnMet SEQ ID NO:128;
GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and
GlyGlySerAspMetAlaGly SEQ ID NO:130.

5. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 1.

6. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 2.

7. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 3.

8. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 3 selected from the group consisting of;

SEQ ID NO:60; SEQ ID NO:61; SEQ ID NO:62; SEQ ID NO:63; SEQ ID NO:64; SEQ ID NO:65; SEQ ID NO:66; SEQ ID NO:67; SEQ ID NO:68; SEQ ID NO:69; SEQ ID NO:70; SEQ ID NO:71; SEQ ID NO:72; SEQ ID NO:73; SEQ ID NO:74; SEQ ID NO:75; SEQ ID NO:76; SEQ ID NO:77; SEQ ID NO:78; SEQ ID NO:79; SEQ ID NO:80; SEQ ID NO:81; SEQ ID NO:82; SEQ ID NO:83; SEQ ID NO:84; SEQ ID NO:85; SEQ ID NO:86; SEQ ID NO:87; SEQ ID NO:88; SEQ ID NO:89; SEQ ID NO:90; SEQ ID NO:91; SEQ ID NO:92; SEQ ID NO:93; SEQ ID NO:94; SEQ ID NO:95; SEQ ID NO:96; SEQ ID NO:97; SEQ ID NO:98; SEQ ID NO:99; SEQ ID NO:100; SEQ ID NO:101; SEQ ID NO:102; SEQ ID NO:103; SEQ ID NO:104; SEQ ID NO:105; SEQ ID NO:106; SEQ ID NO:107; SEQ ID NO:108; SEQ ID NO:109; SEQ ID NO:110; SEQ ID NO:111; SEQ ID NO:112; SEQ ID NO:113; SEQ ID NO:114; SEQ ID NO:115; SEQ ID NO:116; SEQ ID NO:117; SEQ ID NO:118 and SEQ ID NO:119.

9. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 4.

10. A method of producing a EPO receptor agonist polypeptide comprising: growing under suitable nutrient conditions, a host cell transformed or transfected with a replicable vector comprising said nucleic acid molecule of claim 5, 6, 7, 8 or 9

in a manner allowing expression of said EPO receptor agonist polypeptide and recovering said EPO receptor agonist polypeptide.

11. A composition comprising; a EPO receptor agonist polypeptide according to claim 1, 2, 3 or 4; and a pharmaceutically acceptable carrier.

12. A composition comprising; a EPO receptor agonist polypeptide according to claim 1, 2, 3 or 4; a factor; and a pharmaceutically acceptable carrier.

13. The composition of claim 12 wherein said factor is selected from the group consisting of: GM-CSF, G-CSF, c-mpl ligand, M-CSF, IL-1, IL-4, IL-2, IL-3, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3/flk2 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor, IL-3 variants, fusion proteins, G-CSF receptor agonists, c-mpl receptor agonists, IL-3 receptor agonists, multi-functional receptor agonists.

14. A method of stimulating the production of hematopoietic cells in a patient comprising the step of; administering a EPO receptor agonist polypeptide of claim 1, 2, 3 or 4, to said patent.

15. A method for selective ex vivo expansion of erythroid progenitors, comprising the steps of;

(a) culturing erythroid progenitor cells in a culture medium, comprising; a polypeptide of claim 1, 2, 3 or 4; and

(b) harvesting said cultured cells.

16. A method for selective ex vivo expansion of erythroid progenitors, comprising the steps of;

(a) separating erythroid progenitor cells from other cells;

(b) culturing said separated erythroid progenitor cells with a selected culture medium comprising a polypeptide of claim 1, 2, 3 or 4; and

(c) harvesting said cultured cells.

17. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

(a) removing erythroid progenitor cells;

(b) culturing said erythroid progenitor cells in a culture medium, comprising; a polypeptide of claim 1, 2, 3 or 4;

(c) harvesting said cultured cells; and

(d) transplanting said cultured cells into said patient.

18. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

(a) removing erythroid progenitor cells;

(b) separating erythroid progenitor cells from other cells;

(c) culturing said separated erythroid progenitor cells with a selected culture medium comprising a polypeptide of claim 1, 2, 3 or 4;

(d) harvesting said cultured cells; and

(e) transplanting said cultured cells into said patient.

19. A method of claim 15 wherein said erythroid progenitor cells are isolated from peripheral blood.

20. A method of claim 16 wherein said erythroid progenitor cells are isolated from peripheral blood.

21. A method of claim 17 wherein said erythroid progenitor cells are isolated from peripheral blood.

22. A method of claim 18 wherein said erythroid progenitor cells are isolated from peripheral blood.

FIG.1

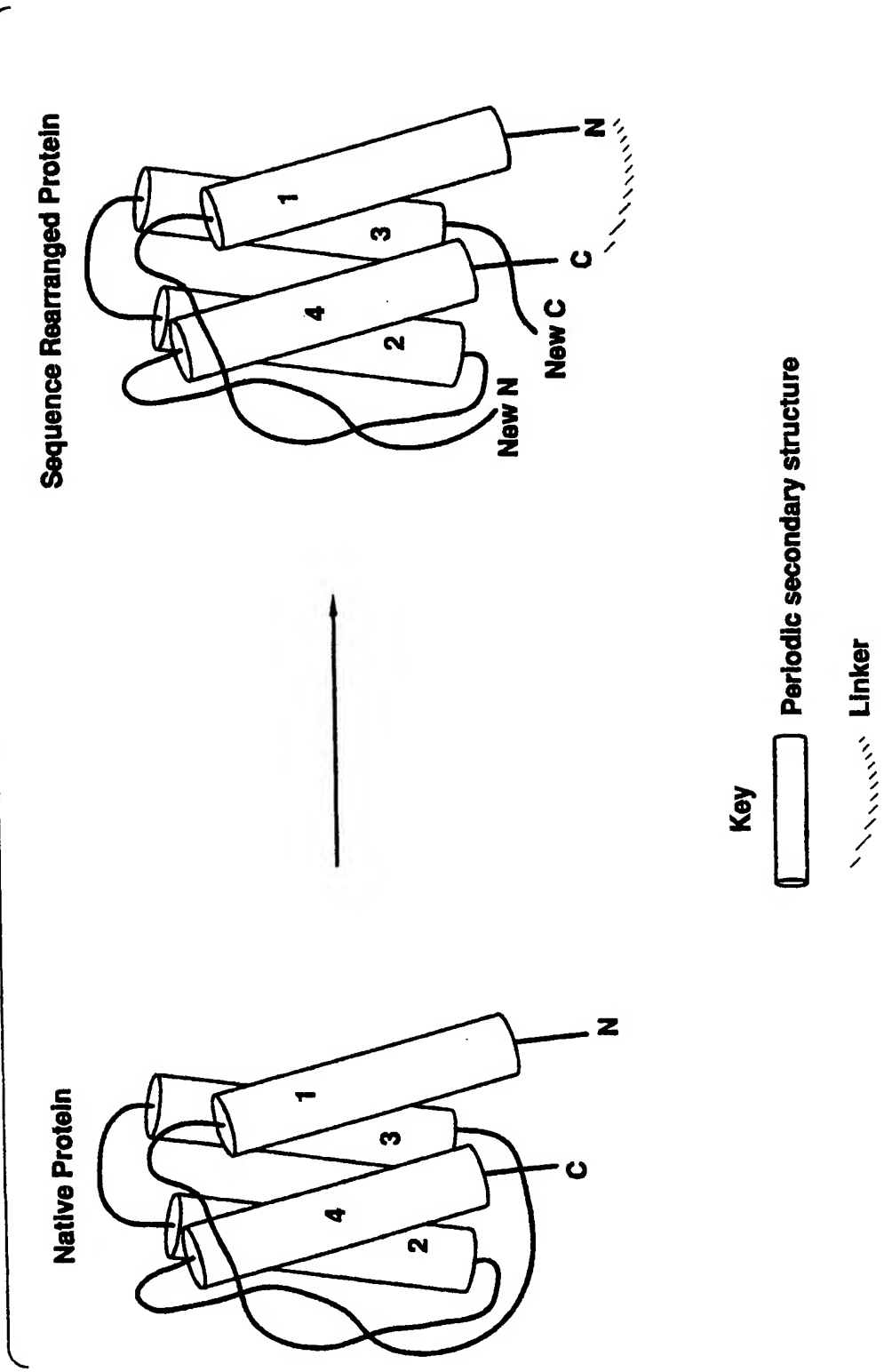
Sequence Rearranged Protein
N
C
New C
New N
1
3
4
2
Native Protein
N
C
1
3
4
2
Key
Periodic secondary structure
Linker

FIG.2

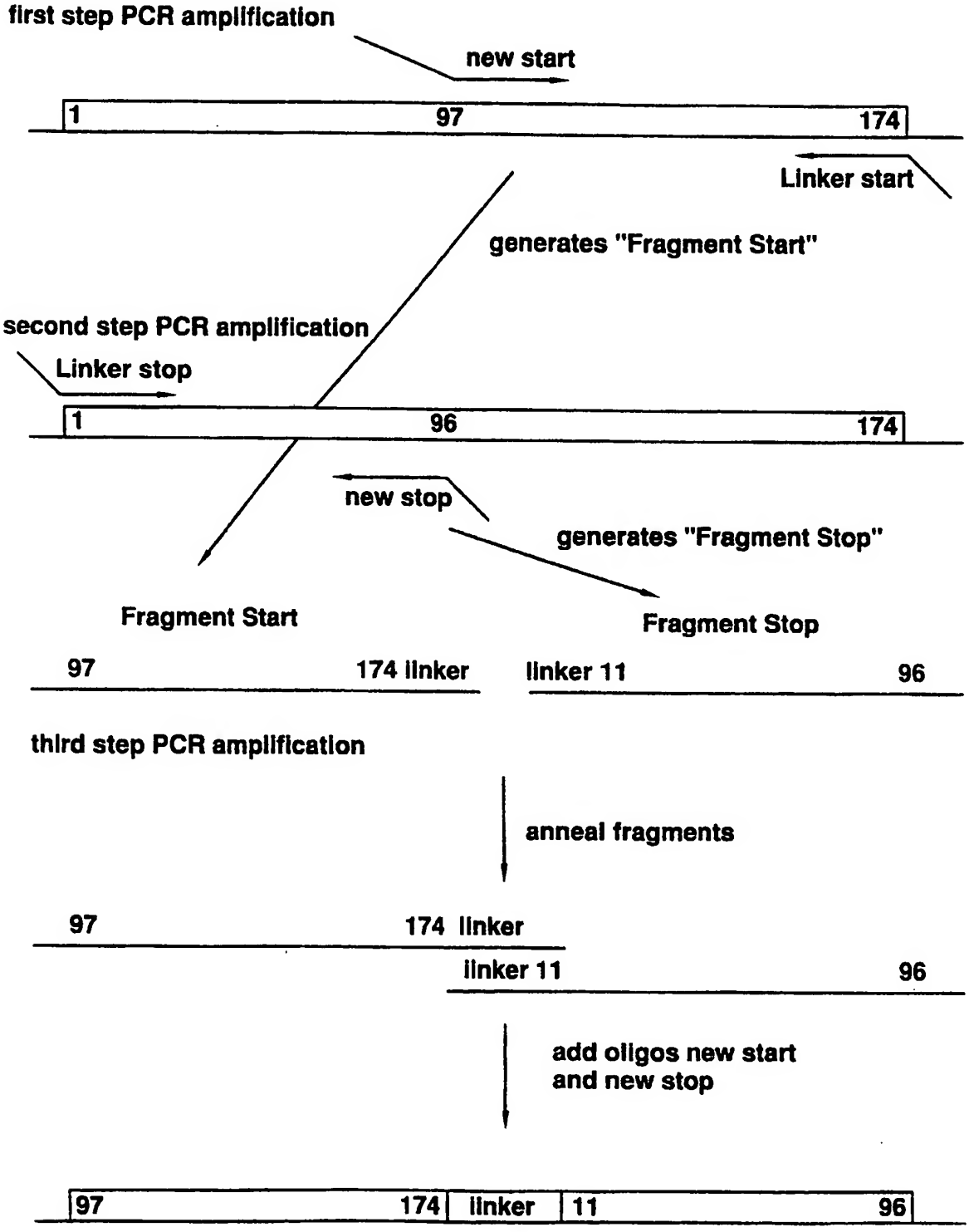
first step PCR amplification
new start
1
97
174
Linker start
generates "Fragment Start"
second step PCR amplification
Linker stop
1
96
174
new stop
generates "Fragment Stop"
Fragment Start
Fragment Stop
97
174 linker
linker 11
96
third step PCR amplification
anneal fragments
97
174 linker
linker 11
96
add oligos new start
and new stop
97
174
linker
11
96

FIG.3

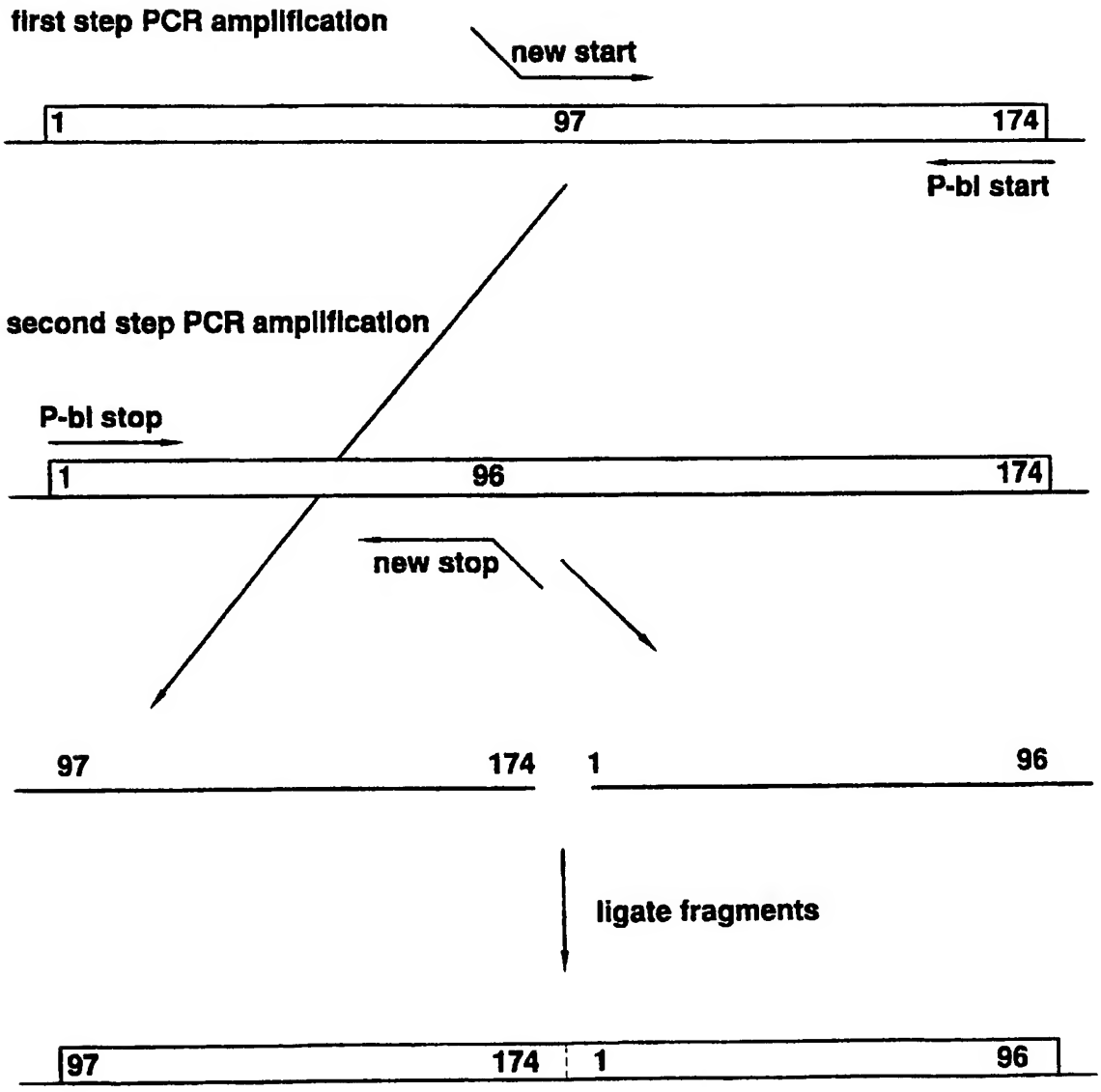
first step PCR amplification
new start
1
97
174
P-bl start
second step PCR amplification
P-bl stop
1
96
174
new stop
97
174
1
96
ligate fragments
97
174
1
96

FIG.4

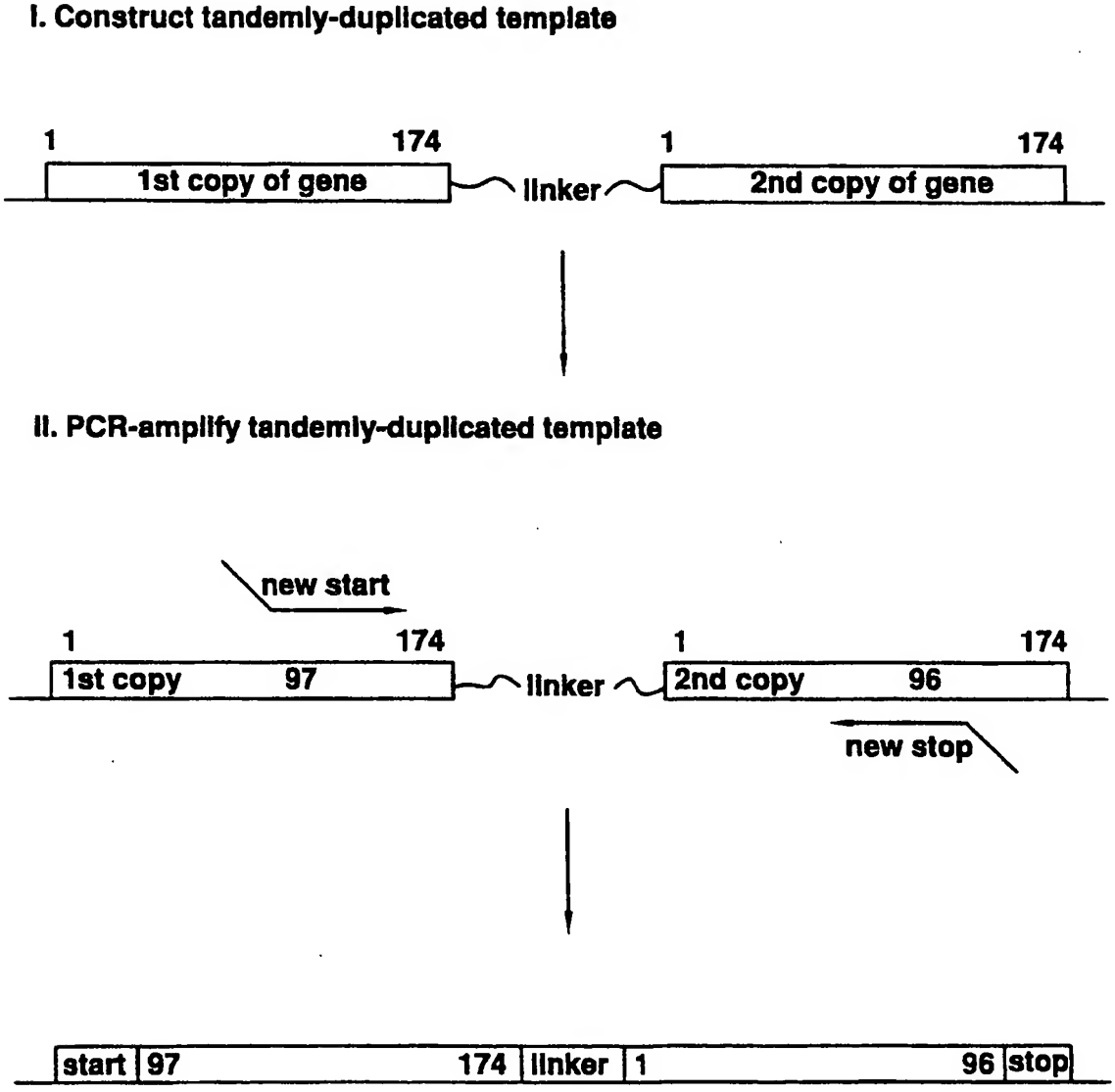
I. Construct tandemly-duplicated template
1
174
1st copy of gene
linker
1
174
2nd copy of gene
II. PCR-amplify tandemly-duplicated template
new start
1
174
1st copy
97
linker
1
174
2nd copy
96
new stop
start
97
174
linker
1
96
stop

FIG.5A

```
    GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAG
  1 ---------+---------+---------+---------+---------+---------+ 60
    CGGGGTGGTGCGGAGTAGACACTGTCGGCTCAGGACCTCTCCATGGAGAACCTCCGGTTC
    AlaProProArgLeuIleCysAspSerArgValLeuGluArgTyrLeuLeuGluAlaLys

    GAGGCCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACT
 61 ---------+---------+---------+---------+---------+---------+ 120
    CTCCGGCTCTTATAGTGCTGCCCGACACGACTTGTGACGTCGAACTTACTCTTATAGTGA
    GluAlaGluAsnIleThrThrGlyCysAlaGluHisCysSerLeuAsnGluAsnIleThr

    GTCCCAGACACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCC
121 ---------+---------+---------+---------+---------+---------+ 180
    CAGGGTCTGTGGTTTCAATTAAAGATACGGACCTTCTCCTACCTCCAGCCCGTCGTCCGG
    ValProAspThrLysValAsnPheTyrAlaTrpLysArgMetGluValGlyGlnGlnAla

    GTAGAAGTCTGGCAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTG
181 ---------+---------+---------+---------+---------+---------+ 240
    CATCTTCAGACCGTCCCGGACCGGGACGACAGCCTTCGACAGGACGCCCCGGTCCGGGAC
    ValGluValTrpGlnGlyLeuAlaLeuLeuSerGluAlaValLeuArgGlyGlnAlaLeu

    TTGGTCAACTCTTCCCAGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGT
241 ---------+---------+---------+---------+---------+---------+ 300
    AACCAGTTGAGAAGGGTCGGCACCCTCGGGGACGTCGACGTACACCTATTTCGGCAGTCA
    LeuValAsnSerSerGlnProTrpGluProLeuGlnLeuHisValAspLysAlaValSer
```

FIG.5B

```
                                                                  GGCCTTCGCAGCCTCACCACTCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCC
301 ----------+----------+----------+----------+----------+----------+ 360
    CCGGAAGCGTCGGAGTGGTGAGACGAAGCCCGAGACCCTCGGGTCTTCCTTCGGTAGAGG
    GlyLeuArgSerLeuThrThrLeuLeuArgAlaLeuGlyAlaGlnLysGluAlaIleSer

                                                                  CCTCCAGATGCGGCCTCAGCTGCTCCACTCCGAACAATCACTGCTGACACTTTCCGCAAA
361 ----------+----------+----------+----------+----------+----------+ 420
    GGAGGTCTACGCCGGAGTCGACGAGGTGAGGCTTGTTAGTGACGACTGTGAAAGGCGTTT
    ProProAspAlaAlaSerAlaAlaProLeuArgThrIleThrAlaAspThrPheArgLys

                                                                  CTCTTCCGAGTCTACTCCAATTTCCTCCGGGAAAGCTGAAGCTGTACACAGGGAGGCCC
421 ----------+----------+----------+----------+----------+----------+ 480
    GAGAAGGCTCAGATGAGGTTAAAGGAGGCCCCTTTCGACTTCGACATGTGTCCCCTCCGG
    LeuPheArgValTyrSerAsnPheLeuArgGlyLysLeuLysLeuTyrThrGlyGluAla

                                                                  TGCAGGACAGGGGACAGATGA
481 ----------+----------+-- 501
    ACGTCCTGTCCCCTGTCTACT
    CysArgThrGlyAspArg
```

INTERNATIONAL SEARCH REPORT

Internat ' Application No
PCT/US 97/18703

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/18 C07K14/505 C07K14/52 A61K38/18 C12N5/10 C12N5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 27732 A (US HEALTH ;PASTAN IRA (US); KREITMAN ROBERT J (US)) 19 October 1995 see abstract; claims 1-51; figures SEQ.54-57 ---	1-13,15, 16,19-22
Y	WO 92 06116 A (ORTHO PHARMA CORP) 16 April 1992 see page 2, paragraph 3; claims 1-26; figure SEQ.3 ---	1-13,15, 16,19-22
A	VIGUERA AR ET AL: "The order of secondary structure elements does not determine the structure of a protein but does affect its folding kinetics." J MOL BIOL, APR 7 1995, 247 (4) P670-81, ENGLAND, XP002056595 cited in the application see the whole document --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
23 February 1998	11. 03. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gurdjian, D

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INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/US 97/18703

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HORLICK R A ET AL: "PERMUTEINS OF INTERLEUKIN 1 BETA-A SIMPLIFIED APPROACH FOR THE CONSTRUCTION OF PERMUTATED PROTEINS HAVING NEW TERMINI" PROTEIN ENGINEERING, vol. 5, no. 5, 1992, pages 427-431, XP002022097 see the whole document ---	1-13
A	KREITMAN R J ET AL: "A CIRCULARLY PERMUTED RECOMBINANT INTERLEUKIN 4 TOXIN WITH INCREASED ACTIVITY" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 91, no. 15, July 1994, pages 6889-6893, XP002022099 see the whole document ---	1-13
A	WO 95 21197 A (SEARLE & CO ;BAUER CHRISTOPHER S (US); ABRAMS MARK ALLEN (US); BRA) 10 August 1995 see page 1 - page 33 -----	1-13,15, 16,19-22

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INTERNATIONAL SEARCH REPORT

Inte. .ional application No.
PCT/US 97/18703

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/18703

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 14 17 18 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna l Application No
PCT/US 97/18703

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9527732 A	19-10-95	US 5635599 A	03-06-97
		AU 2285795 A	30-10-95
		CA 2187283 A	19-10-95
		EP 0754192 A	22-01-97
WO 9206116 A	16-04-92	AU 1157695 A	13-04-95
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		CA 2069746 A	29-03-92
		EP 0503050 A	16-09-92
		JP 5502463 T	28-04-93
		ZA 9107766 A	29-03-93
WO 9521197 A	10-08-95	AU 1680595 A	21-08-95
		EP 0742796 A	20-11-96
		JP 9508524 T	02-09-97